AN INVESTIGATION OF URIDINE ON DEPRESSIVE SYMPTOMS AND NEUROPSYCHOLOGICAL TEST PERFORMANCE IN YOUTH AGES 13-21 WITH BIPOLAR DISORDER

by

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ABSTRACT

The current study was designed to examine the effects of uridine on depressive symptoms and neuropsychological test performance in depressed youth with bipolar disorder. Participants included 20 adolescents diagnosed with bipolar depression between the ages of 13 and 21. Additionally, this study sought to compare depressed bipolar youth to an age- and gender-matched unaffected comparison group. Therefore, 10 unaffected comparison adolescents also participated in the study. Recruitment of participants took place between 2014-2015 at a university-based psychiatric hospital. All youth and their families provided consent to participate in the study and were administered a diagnostic clinical interview. Mood was assessed weekly throughout the study using rating scales and neuropsychological tests were administered pre- and posttreatment. Bipolar participants were randomized to treatment with 500mg twice daily of uridine or placebo. Three participants were removed from the data analyses (2 in the uridine group and 1 in the placebo group) due to noncompliance.

Results of the study demonstrated that uridine was tolerated and there were no serious adverse events. Three participants (33%) in the uridine vs. four participants (50%) in the placebo group showed reduced depression symptoms. However, there were no significant differences between the placebo and uridine groups on depression ratings from pre- to posttreament. Additionally, there were no differences in neurocognitive performance between the uridine or placebo groups from pre- to posttreatment.

Importantly, treatment with uridine did not have any negative effects on neurocognitive performance; however, these results did not suggest any neuropsychological benefits either. Bipolar participants showed more impairment in attention, executive functioning, and processing speed than unaffected comparison participants at baseline. Academic experiences for bipolar participants were different from comparison participants and included more academic difficulties, discontinuations, and transfers to new schools and programs. Participants who reported academic difficulties or received special education services performed lower on attention, working memory, executive functioning, and processing speed tasks. Without more subjects, no firm conclusions can be drawn from the current findings; however, these findings suggest a need for further research into uridine treatment. Treatment of adolescent bipolar disorder is complex and treatments specifically designed for youth are needed.

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CHAPTER I

INTRODUCTION

Approximately 1 to 2% of children and adolescents worldwide are affected by bipolar disorder (Youngstrom, Freeman, & Jenkins, 2009). Bipolar disorder (BD) in youth is characterized by abrupt mood swings of depression, mania, or hypomania (American Psychiatric Association, 2013). Youth with BD also experience euthymic episodes, which are states that are absent of manic/depressive symptoms. In addition, children and adolescents with BD often exhibit cognitive deficits that can interfere with their social functioning and academic performance and have been shown to have a significant, and negative, effect on long-term outcomes (Burdick, Goldberg, & Harrow, 2010; Dickstein et al., 2004). Specifically, researches have found impairments in the areas of attention, executive function, working memory, verbal learning, spatial memory, and processing speed among youth with BD (Pavuluri, West, Hill, Jindal, & Sweeney, 2009).

It was initially believed that individuals with BD did not experience cognitive impairments during the euthymic state; however, researchers have found evidence of neuropsychological deficits during both a depressed and euthymic mood state (Basso, Lowery, Ghormley, & Bornstein, 2001). Neuropsychological deficits that persist across mood states have particular importance in terms of outcomes for individuals with BD

(Malhi et al., 2007). Nonetheless, there are no approved medication treatments for BD that have been shown to reduce the potential for cognitive impairment associated with drug therapy.

Bipolar disorder (BD) in children and adolescents is understudied and treatments specifically designed specifically for youth are needed (Liu et al., 2011). Guidelines for treatment of youth with BD recommend using pharmacological intervention prescribed for adults (McClellan, Kowatch, & Findling, 2007). While medication is often the first line of treatment, it can have serious deleterious side effects. For example, lithium and antipsychotic medications used to treat BD have been associated with sedation, weight gain, headaches, dyskinesia, tics, tremors, and, when used by females, ovarian cysts (Blader & Kafantaris, 2007; Liu et al., 2011).

In addition to concerns regarding safety, there are questions regarding the efficacy of medications for treating youth with BD. While lithium and antipsychotics have shown efficacy in treating youth with BD, at least 50% of adolescents experience symptom recurrence within 18 months (Birmaher et al., 2006). Some youth with BD are non-responsive to medications, experience intolerable side effects, or require a combination of treatments to get desired effects (Pavuluri, 2008). All of these difficulties often lead to poor treatment adherence, which can further reduce the effectiveness of pharmacological intervention. A 12-month study following first hospitalization after a manic or mixed episode revealed that only 35% percent of adolescents with BD had full adherence to prescribed medications (DelBello, Hanseman, Adler, Fleck, & Strakowski, 2007). Furthermore, psychotropic medications and mood stabilizers may worsen neuropsychological impairments that youth with BD experience (Dias et al., 2012; Macqueen & Young, 2003).

One of the treatments that have been used during a depressed state of BD is uridine. Uridine is a naturally occurring pyrimidine nucleoside that is essential for RNA synthesis and is a critical element in the regulation of cellular energetics (Wurtman, Cansev, Sakamoto, & Ulus, 2010). Pyrimidines have been investigated in treating depressive disorders since the mid-1970s (Salvadorini, Galeone, Nicotera, Ombrato, & Saba, 1975). Nucleosides have been shown to be effective for treating disorders such as BD that are related to mitochondrial dysfunction (Saydoff et al., 2013). Following a 6-week oral administration of 500 mg of uridine twice daily, 7 depressed adolescents with BD showed a 54% decrease in depression ratings on the Children's Depression Rating Scale-Revised (CDRS-R) (Kondo et al., 2011).

Furthermore, there are data that have shown uridine to increase cognitive and neuropsychological functioning in some patients with Alzheimer's disease (Mi, van Wijk, Cansev, Sijben, & Kamphuis, 2013; Saydoff et al., 2013). It is, therefore, hypothesized that uridine, when used as a treatment for depression in adolescents with BD, can have neuropsychological benefits. The effects of uridine administration on neuropsychological test performance for individuals with BD have not yet been evaluated. The purpose of this study is to investigate effects of uridine in the treatment of BD on depressive symptoms and neuropsychological test performance in youth.

Bipolar Disorder in Youth

Historically, BD has been reported to occur in late adolescence and early adulthood. During the early 20th century, BD was reported by Emil Kraepelin to occur most frequently in youth ages 15 to 20 years of age (Kraepelin, 1921). Subsequent studies have shown that as many as 60% of adults with BD experienced symptoms before the age

of 20 and 10-20% of individuals with BD reported symptoms before the age of 10 (Washburn, West, & Heil, 2011). Recently, there has been an increase in the diagnosis of children with "pediatric" BD who display severe irritability and mood dysregulation before the age of 10, leading to a debate about symptomatology and treatment of BD in youth (Parens & Johnston, 2010).

From 1994-1995 to 2002-2003, there was a 4,000% increase in the diagnosis of BD in youth (Moreno et al., 2007). It is not known whether this increase was due to greater awareness of the disorder in children, a change in the diagnostic criteria from the DSM-III to the DSM-IV, influence of the pharmaceutical industry, or an actual increase in BD in youth (Parry & Levin, 2012). Regardless of the reason, the increase in pediatric BD has led to younger children being treated with medication, and subsequent concern regarding overmedication and adverse drug side effects.

The American Psychiatric Association (APA) has attempted to address these issues in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders, or the DSM-5. Specifically, recent changes to pediatric bipolar disorder in the DSM-5 have brought about questions regarding the future of diagnosis and treatment of BD in youth. The DSM-5 eliminated the diagnosis of pediatric BD and introduced a new diagnostic category called Disruptive Mood Dysregulation Disorder (DMDD). DMDD is characterized by severe temper or aggressive outbursts, persistent irritable/negative mood that is observable by others between outbursts, and symptoms that have persisted for 12 months prior to age 10. According to APA, the adoption of the DMDD diagnosis is an attempt to improve reliable and valid diagnosis and the treatment of children with mental health problems, and avoid over-diagnosis and overmedication of children (American Psychiatric Association, 2013). However, there are concerns regarding the limited scope

of research that preceded the new classification of DMDD, the lack of clinical guidelines/stability regarding diagnosis, and symptom overlap with other disorders; in particular, BD, Oppositional Defiant Disorder, and Conduct Disorder (Axelson et al., 2012). Despite the removal of pediatric BD from the DSM-5, the diagnosis of BD still exists for individuals ages 10 and older. It should be noted that for the current study, the term "youth" will be used to describe individuals ages 13 to 21, not just 10 or older.

Symptomatology and Course

Youth with bipolar disorder experience mood episodes of depression, mania/hypomania, and euthymia. Depression is defined as having a consistently depressed mood or loss of pleasure in daily activities for at least a 2-week period. The depressed mood impairs social and occupational functioning and is characterized by five or more of the following symptoms: depressed mood, loss of pleasure in activities, change in appetite, change in sleep, psychomotor retardation/agitation, fatigue, feelings of worthlessness/excessive guilt, inability to concentrate/indecisiveness, and/or recurrent thoughts of death (American Psychiatric Association, 2013).

Mania is characterized by abnormally elevated or irritable mood for a period of at least 1 week with three of the following symptoms: grandiosity, decreased need for sleep, pressured speech, increase in goal-directed activity, racing thoughts, distractibility, and involvement in pleasurable activities. A severe episode of mania may cause impairment in occupational or social functioning, require hospitalization, or may include psychotic features. Bipolar I disorder is characterized by the occurrence of one or more manic episodes and often one or more depressive episodes. In contrast, hypomania is characterized by episodes of mania in which the duration is shorter and the mood episode

is usually less severe and does not cause serious impairment in functioning that requires hospitalization. Additionally, psychotic symptoms are not present during hypomania. Individuals who experience hypomanic episodes are diagnosed with bipolar II disorder. During a euthymic state, youth with BD do not experience symptoms of depression or mania/hypomania.

Youth with bipolar disorder can switch from one mood episode to another. For example, approximately 60-70% of manic and hypomanic episodes occur immediately before or after a major depressive episode. If four or more mood episodes occur within a year, this is considered rapid cycling. The average age of onset for BD is 18 years of age. BD is a recurrent disorder and has a chronic course. More than 90% of individuals who experience a single manic episode will have additional manic episodes (American Psychiatric Association, 2013).

Children and adolescents with BD experience different symptomatology than adults. For example, youth display more irritability and aggression while adults with BD tend to show more elation and grandiosity during mania (Safer, Magno Zito, & Safer, 2012). BD that occurs in youth is worse than BD that occurs in adults with regard to mood symptoms and dysregulation. For example, the beginning of a manic episode for a child may be difficult to determine because the symptoms are different than those displayed by adults. Youth with BD display more symptoms of irritability during mania and they are more likely to abruptly to switch moods. However, as youth with BD become older, their mood episodes become more defined (American Psychiatric Association, 2013).

Prevalence Rates and Comorbidities

The rates of BD are difficult to establish in youth; however, estimates suggest that between 1-2% of children worldwide have bipolar disorder (American Psychiatric Association, 2013). BD is more commonly diagnosed in high-income than in low-income countries (Ormel et al., 2008) and family history of BD is one of the strongest and most consistent risk factors. For first-degree relatives of individuals with BD, the risk of having BD is increased 10 times. Bipolar disorder is found equally in women and men, although gender appears to affect the type and number of mood episodes. The first mood episode in men is typically a manic episode, whereas women tend to experience a major depressive episode first. Overall, men are likely to have an equal number of manic and depressive episodes, while women experience more depressive episodes. Furthermore, rapid cycling is more common in women than in men (American Psychiatric Association, 2013).

Children and adolescents with BD often experience other psychological problems such as attention deficit hyperactivity disorder (ADHD), conduct disorder (CD), anxiety disorders, and substance use disorders. Anxiety disorders may include social phobia, panic attacks, and specific phobias. Studies have found a wide range in comorbidity rates for youth with BD in their samples, ranging from 11 to 75% for ADHD, 5 to 37% for CD, 12 to 56% for anxiety disorders, and 0 to 40% for substance use disorders (Pavuluri, Birmaher, & Naylor, 2005). Additionally, pediatric BD is found to be comorbid in 11% of children with Asperger's disorder (Wozniak et al., 1997). Age appears to have an effect on comorbidity with different disorders. Substance abuse has been found to be 8.8 times higher in adolescents than in children with BD (Wilens et al., 2004), while the rate of comorbid ADHD is higher in pediatric bipolar disorder than in adolescent bipolar

disorder (Findling et al., 2001). Individuals with BD in general are at a higher risk for suicidality; according to the American Psychiatric Association (2013), the rate of attempted suicide in BD ranges from 32 – 36%, and bipolar disorder may account for one quarter of all completed suicides. For individuals with bipolar II disorder, the lethality of attempts may be higher than in individuals with bipolar I disorder.

Neuropsychological Deficits in Youth With Bipolar Disorder

Neurocognitive problems in adults with BD have been recognized for over 50 years. Interest in youth with BD has increased over the past 10 years, and a growing body of literature now documents different cognitive deficits occurring in youth compared to those observed in adults (Joseph, Frazier, Youngstrom, & Soares, 2008; Pavuluri et al., 2005). Specifically, recent studies examining neurocognitive deficits in youth have identified deficits in attention, executive function, memory, and processing speed (Pavuluri et al., 2009). Neurocognitive functioning in youth with BD may have a large impact on academic and/or social performance, and affect further development. Therefore, several studies have investigated functioning and outcomes related to neuropsychological deficits (Burdick et al., 2010; Cahill, Green, Jairam, & Malhi, 2007; Malhi et al., 2007). Recent findings in these areas are described.

Attention

Youth with BD have been reported to demonstrate deficits in attention and vigilance (McClure et al., 2005). Several studies have investigated attentional capacity in youth with BD (Doyle et al., 2005; McClure et al., 2005; Pavuluri et al., 2009). Youth with BD performed more poorly in comparison to unaffected controls on the Continuous

Performance Test (CPT), a computerized test that is widely used to assess visual attention (Pavuluri, O'Connor, Harral, Moss, & Sweeney, 2006; Pavuluri et al., 2009). Doyle and colleagues (2005) used an auditory CPT with 57 participants with BD and 46 unaffected age- and gender-matched controls and demonstrated that participants with BD also performed significantly worse than controls on auditory CPT.

Executive Functioning

Another area of neuropsychological impairment in youth is executive functioning (EF). Outcomes for EF have traditionally been based on measures of set shifting, response inhibition, planning, and verbal fluency. The Wisconsin Card Sorting Task (WCST), the Trail Making Test (TMT-B), and the Intra-Dimensional/Extra Dimensional Set-Shift Subtest are measures of set shifting, or the ability to switch attention to different stimuli and show cognitive flexibility. Youth with BD performed worse on the WCST compared to both an unaffected control group (Meyer et al., 2004) and unaffected siblings (Doyle et al., 2009). Three studies have demonstrated set shifting deficits in youth with BD on the TMT-B (Bearden, Woogen, & Glahn, 2010; Pavuluri, O'Connor, et al., 2006; Pavuluri et al., 2009) and performance was more impaired for youth with BD than unaffected peers on the Cambridge Neuropsychological Test Automated Battery (CANTAB) Intra-Dimensional/Extra Dimensional Set-Shift Subtest (ID/ED shift) (Dickstein et al., 2007; Dickstein et al., 2004).

Response inhibition, or suppression of an automatic action, is another aspect of executive function that has been found to be impaired in youth with BD (Doyle et al., 2005). Youth with BD performed worse on a measure of response inhibition, the Stroop task, than unaffected controls (Doyle et al., 2005). The Controlled Oral Association Test

(COWAT) is often used to assess verbal fluency, or rapid retrieval of words from memory. Youth with BD demonstrated verbal fluency deficits when compared to unaffected controls on the COWAT (Pavuluri, O'Connor, et al., 2006; Pavuluri et al., 2009). A 3-year follow-up study by Pavuluri and colleagues (2006) revealed impairment in the development of this aspect of executive functioning for youth with BD. Youth with BD showed improvements in executive functioning over time; however, performance lagged behind when compared to unaffected peers (Pavuluri, O'Connor, et al., 2006).

Memory

Three areas of memory have been found to be impaired in youth with BD: working memory, verbal memory, and visual-spatial memory. Of these areas, verbal memory appears to be most affected across all mood episodes in BD (Cavanagh, Van Beck, Muir, & Blackwood, 2002). Since learning is affected by the ability to organize and encode information into memory, verbal memory deficits may impair learning and academic performance in youth with BD. Youth with BD did not perform as well as unaffected controls on the California Verbal Learning Test - Child version (CVLT-C), a list-learning task that assess verbal memory (Pavuluri, O'Connor, et al., 2006; Pavuluri et al., 2009) or as well as unaffected controls and unaffected siblings on the CVLT-II (Doyle et al., 2009). In a study of 21 BD subjects, Glahn et al. (2005) found impaired verbal memory for BD I subjects; however, the scores of subjects with BD II and BD-not otherwise specified (NOS) did not differ from unaffected controls.

Working memory deficits have also been investigated in youth with BD. The Wechsler Memory scales have been used to examine working memory using the Arithmetic, Digit Span, and Spatial Span subtests. Using the Wechsler Memory Scales,

youth with BD show working memory impairment when compared to controls (Pavuluri, O'Connor, et al., 2006; Pavuluri et al., 2009) as well as unaffected siblings (Doyle et al., 2009). Dickstein et al. (2004) used the CANTAB spatial memory span with 21 BD youth and 21 unaffected controls and found impaired working memory for youth with BD.

Visual-spatial memory is also affected in youth with BD. Deficits in visual-spatial memory were demonstrated by youth with BD compared to controls on performance on the Wide Range Assessment of Memory and Learning (WRAML) (Rucklidge, 2006) and the Spatial Working Memory Capacity Task (SCAP) (Bearden et al., 2010; Pavuluri, Schenkel, et al., 2006). Facial memory has also been shown to be impaired for youth with BD on the Test of Memory and Learning (TOMAL) (Olvera, Semrud-Clikeman, Pliszka, & O'Donnell, 2005). Results on the Penn Face Memory Test demonstrated impairment in youth with BD in the visual memory domain, due to worse performance on a face recognition task when compared to unaffected controls (Pavuluri et al., 2009).

Processing Speed

Processing speed, which is critical for learning, academic performance, and everyday functioning, is also affected in youth with BD. Impairments in processing speed have been assessed using the Digit Symbol/Coding subtests of the Wechsler scales. Youth with BD performed worse on these subtests of the WISC-III when compared to unaffected controls (Doyle et al., 2005; Doyle et al., 2009). Deficits in processing speed have also been identified in youth with BD using the TMT-A (Pavuluri et al., 2005; Pavuluri et al., 2009). A longitudinal study of youth with BD revealed that processing speed deficits are associated with poor global functioning and social adaptation (Burdick et al., 2010).

Neuropsychological Deficits in Mood States

Recent research has explored neurocognitive deficits in BD youth, but few studies have controlled for mood state. Most of what is known about neuropsychological functioning in BD in different mood states is from research with adults. Evaluation of neurocognitive deficits during different mood episodes has revealed that impairment persists during euthymic states (e.g., Malhi et al., 2007; Robinson & Ferrier, 2006). Robinson and Ferrier, for example, demonstrated that subjects with BD experienced greater verbal memory impairment during mania, whereas Malhi et al. showed evidence of greater neuropsychological impairment during a depressed episode. This section describes the most recent findings regarding neuropsychological deficits of individuals with BD that are associated with each mood episode: depressive, manic, and euthymic.

During a depressive episode, adults with BD have demonstrated impairments across all neurocognitive domains (Malhi et al., 2007). Deficits in sustained attention, set shifting, memory, and executive functioning have been associated with depressive episodes in BD (Trichard et al., 1995). Problems with verbal fluency, verbal recall, and recognition were also found in BD adults who were in a depressed state (Ali et al., 2001). Researchers using the Controlled Oral Word Association Test (COWAT) found that verbal fluency is worse for adults during a depressive episode than during an euthymic state (Martinez-Aran et al., 2004). Adults with BD have also demonstrated impaired problem solving, concept formation, and decision making during depressive episodes (Sweeney, Kmiec, & Kupfer, 2000). Poor psychosocial functioning was found to be associated with slow processing speed and reaction time during a depressive episode in adults with BD (Malhi et al., 2007). Several studies have compared bipolar and unipolar individuals during depressive episodes. Adults with unipolar and bipolar depression have

demonstrated memory and concentration impairments that may affect verbal learning (Ali et al., 2001). Moreover, adults with BD have impaired performance in verbal fluency and executive functioning compared with adults with unipolar depression (Borkowska & Rybakowski, 2001).

Few studies have been conducted on individuals with BD during a manic/hypomanic episode; however, recent findings suggest that they are impaired in executive functioning. In particular, BD adults in a manic state have been found to experience difficulty with planning, set shifting, concept formation, and problem solving. Such individuals have demonstrated significant impairment on the CPT, which suggests difficulty with sustained attention and response inhibition (Strakowski et al., 2005). Reduced psychosocial functioning during hypomania has been associated with poor working memory and new learning (Malhi et al., 2007). Verbal memory and learning deficits during mania are thought to be related to an encoding deficit (Fleck et al., 2003). Spatial deficits and spatial memory impairments have been reported in adults with manic or mixed symptoms (Sweeney et al., 2000). Episodic memory deficits associated with mania have also been demonstrated in adult BD (McGrath, Chapple, & Wright, 2001).

During an absence of mood symptoms, a euthymic state, research indicates that neuropsychological impairments still persist, although they are not as severe as those that occur during episodes of mania or depression. During a euthymic state, adults with BD continue to show deficits in executive functioning and verbal memory (Malhi et al., 2007). McClure et al. (2005) demonstrated verbal memory deficits using the Test of Memory and Learning (TOMAL) delayed recall of stories. Adults with BD in a euthymic state have also shown difficulty with sustained attention (Ferrier, Stanton, Kelly, & Scott, 1999). Despite good social adaptation in euthymic episodes, adults with BD may

experience visual-spatial recognition memory impairment (Cahill et al., 2007). During a euthymic state, BD adults made many perseveration errors on the Wisconsin Card Sort Test, which may represent a persistent deficit in cognitive flexibility (Cahill et al., 2007). Adults with BD may also have difficulties with problem solving. For example, adults with BD in a euthymic state relied on specific details rather than general information to solve problems, suggesting impairment in holistic processing (Sapin, Berrettini, Nurnberger, & Rothblat, 1987).

Few studies have compared neuropsychological functioning across mood states; however, existing research indicates that impairment in attention, memory, and verbal fluency may persist across all mood episodes. Furthermore, the methodology used to compare neurocognitive functioning across mood states is complex and has limitations. Longitudinal studies have also shown that neuropsychological deficits may depend on the course of the illness. Burdick et al. (2010) found that the neuropsychological performance of adults with BD was correlated with affective symptoms, history of mood episodes, occupational functioning, and previous hospital admissions. Successive mood episodes that are severe, unstable, or long-lasting may further exacerbate cognitive impairments (Robinson & Ferrier, 2006).

Functional Impairments/Outcomes

Due to neuropsychological impairments, youth with BD may experience challenges that impact their ability to interact socially and perform to their full potential in school and work. Reading and writing difficulties are estimated to occur in about 42-45%, and math difficulties are reported in about 30% of youth with BD (Pavuluri, O'Connor, et al., 2006). Reading and writing impairments in youth with BD have been

found secondary to problems in attention and working/verbal memory, and may be impacted by executive functioning as well (Pavuluri, O'Connor, et al., 2006). Disturbances in attention in BD youth are associated with math difficulties. Neurocognitive impairments in BD youth in the areas of attention, memory, and processing speed have shown to been associated with dysfunctional social and vocational outcomes (Bearden et al., 2010). Processing speed deficits have been associated with poor global functioning and social adaptation (Burdick et al., 2010) and psychosocial functioning in BD has been correlated with poor executive functioning (Malhi et al., 2007).

When individuals with BD are reportedly functioning well, they often still describe difficulty with decision making that requires consideration of future consequences (Malhi et al., 2007). One common example is when individuals with BD discontinue the use of drug therapy after they see improvement in symptoms. Another finding associated with cognitive functioning and outcomes described the influence of verbal learning and memory impairment on occupational status for individuals with BD (Burdick et al., 2010). A longitudinal study by Burdick et al. (2010) of 33 participants with BD at 15 years following hospitalization found that an increase in the number of hospitalizations was associated with poor occupational status. These patients also had nearly three times as many mood episodes as patients with good work outcomes. Symptom management and treatment appear to be critical for improving long-term outcomes in BD.

Treatments for Youth With Bipolar Disorder

Pharmacological Treatments

Current guidelines for treatment of youth with BD recommend medications used by adults with BD (McClellan et al., 2007). These include lithium, mood stabilizers, anticonvulsants, and antipsychotics. Mood stabilizers and anticonvulsants that are used to treat adults with BD have also been used with youth (e.g., lamotrigine, valproate, carbamazepine, topiramate, and divalproex). Atypical antipsychotics that are used to treat BD in youth include olanzapine, quetiapine, risperidone, and aripiprazole. There are two recommended algorithms for pharmacological treatment of BD in youth based on the presence of psychosis. First, traditional mood stabilizers and atypical antipsychotics are suggested for youth with BD I, manic or mixed without psychosis. Combination therapy follows if there is partial or no response. Second, for BD with psychosis, combination therapy with a mood stabilizer and antipsychotic medication is recommended, and continued psychopharmacological treatment may be required to prevent relapse.

To stabilize mood in BD, lithium is considered the gold standard and is often the first line of treatment. Although lithium has shown success in both short-term and long-term treatment, it has been associated with cognitive side effects, including impairment of attention, short-term memory, and psychomotor skills. In a study of 46 BD patients, verbal memory and psychomotor speed were less impaired after 2 weeks of lithium discontinuation (Kocsis et al., 1993) when compared to their performance while taking the medication. Other studies have found contradictory results, and longitudinal studies of lithium use in BD suggest that cognitive dysfunction may not be directly affected by lithium, but rather by the duration of lithium exposure (Wingo, Wingo, Harvey, & Baldessarini, 2009). Reported beneficial effects associated with taking lithium include

reducing the risk of suicide (Tondo & Baldessarini, 2009) and prevention of Alzheimer's disease (Nunes, Forlenza, & Gattaz, 2007).

Despite their effectiveness at stabilizing mood, anticonvulsants have also been associated with memory, attention, and psychomotor impairments (Dias et al., 2012). Sedation, cognitive blunting, and neurotoxicity may occur with higher doses of some anticonvulsants, especially topiramate, valproate, and carbamazepine (Gualtieri & Johnson, 2006). Valproate has shown many negative effects on attention, psychomotor speed, memory, and learning (Gualtieri & Johnson, 2006). Carbamazepine is associated with impairments in memory, attention, and information processing (Gallassi et al., 1988). Topiramate has been linked with deficits in attention, processing speed, verbal fluency, language, perception, and memory (Ketter, Wang, Becker, Nowakowska, & Yang, 2003). Conversely, lamotrigine is an anticonvulsant used during depressive episodes that has few cognitive side effects. In fact, lamotrigine treatment has shown to improve working memory and verbal memory in BD individuals. After 6 weeks of treatment, lamotrigine enhanced cortical functioning involved in memory and emotional regulation in BD individuals (Pavuluri, Passarotti, Mohammed, Carbray, & Sweeney, 2010).

Atypical antipsychotics have been used most frequently in combination with lithium or mood stabilizers. While they are also used as monotherapy, the majority of use is in combination with other medications. Atypical antipsychotics have shown more negative cognitive effects than lithium and anticonvulsants. Olanzapine has been successful for treatment in in all phases of BD, but it is associated with verbal memory impairment (Hammonds & Shim, 2009). Quetiapine has been associated with cognitive impairment and lethargy (Castren & Rantamaki, 2010). In euthymic BD individuals,

risperidone improved executive functioning (Bubser, Byun, Wood, & Jones, 2012).

The use of antidepressants with youth with BD is controversial, as many studies have shown no benefit to adding them to lithium (Dias et al., 2012). Antidepressants vary in their cognitive side effects, but no studies have examined the neuropsychological effects of antidepressants on BD. Tricyclic antidepressants and serotonin and norepinephrine reuptake inhibitors (SNRIs) have been associated with cognitive deficits, although selective serotonin reuptake inhibitors (SSRIs) have been suggested to have neuroprotective properties.

In conclusion, many of the medications that children take to treat BD may affect cognition. Long-term pharmacological treatment can cause further cognitive impairment that may impair functional outcomes (Henin et al., 2007). Pharmacological treatment of youth with BD may require trying several different trials of medications until a successful combination can be found (Pavuluri, 2008). Furthermore, the side effects from medications can further complicate treatment compliance and adherence. Noncompliance with lithium treatment was associated with a 90% relapse rate in adolescents with BD. However, those adolescents with good treatment adherence still experienced 38% relapse 18 months posthospitalization (Strober, Morrell, Lampert, & Burroughs, 1990).

Overview of Uridine Research

Since uridine is found in every human cell, its utilization and transport throughout the body and the brain have been extensively studied (Cansev, 2006). Recently, therapeutic uses of uridine have been examined in both human and animal research. Uridine has been investigated in its pure form, as a prodrug, and more frequently combined with other nutritional supplements.

Uridine has been investigated as the prodrug triacetyluridine (TAU) due to its bioavailability and ability to achieve higher uridine blood levels following oral consumption. Patients with cancer undergoing chemotherapy have received up to 6 grams of TAU four times daily with no adverse affects (Hidalgo et al., 2000). Research has investigated uridine-based compounds in individuals with diabetic neuropathy (Gallai, Mazzotta, Montesi, Sarchielli, & Del Gatto, 1992) and autism (Page & Moseley, 2002). Recently, a uridine compound has been created for the treatment of mitochondrial toxicities related to nucleoside reverse transcriptase inhibitor (NRTI) treatment in HIV patients (Walker & Venhoff, 2005).

Uridine has also been investigated in animal models to test for possible neuroprotective effects in disorders such as Parkinson's, Huntington's, and Alzheimer's diseases. In unmedicated patients with mild Alzheimer's Disease, uridine improved memory performance (Mi et al., 2013). In animal models of Alzheimer's disease, Saydoff et al. (2013) found that improvement in object recognition and social transmission of food preference improved motor behavior and reduced anxiety. Uridine and choline combined increased selective attention and spatial learning in a rodent model designed to test cognitive impairment (De Bruin, Kiliaan, De Wilde, & Broersen, 2003).

Uridine can also be taken orally in the form of Cognizin, an over-the-counter supplement also known as citicoline or CDP choline. After citicoline is ingested, it is converted to choline and uridine in the gut. Studies have demonstrated that after taking CPD choline, blood uridine levels increase (Wurtman, Regan, Ulus, & Yu, 2000). Citicoline has been investigated in the treatment of vascular dementia, stroke, traumatic brain injuries, Parkinson's disease, Alzheimer's disease, and brain aging (Fioravanti & Buckley, 2006). Researchers have examined citicoline in the treatment of cognitive

impairment and there is evidence that it may play a role in improving memory and attention (Fioravanti & Buckley, 2006). For example, 30 patients with mild to moderate Alzheimer's disease received 12 weeks of treatment with 1000 mg of citicoline or placebo. Results demonstrated that patients who received citicoline treatment had better cognitive performance on the Alzheimer's disease Assessment Scale-Cognitive (ADAS-cog) and increased brain bioelectrical activity of the occipital electrodes (Alvarez et al., 1999).

Further, Cognizin has been reported to increase short-term memory and verbal memory in healthy adults (Spiers, Myers, Hochanadel, Lieberman, & Wurtman, 1996). After 6 weeks of Cognizin citicoline administration with healthy adults, there was an increase in cellular synthesis and cellular energy determined by increased PCr and PCr/Pi and PE in the ACC region of the brain (Silveri et al., 2008). Findings by McGlade et al. (2015) revealed that citicoline improved attention and motor speed performance in normal adolescent males in a trial of random assignment to 250 mg, 500 mg, or placebo daily for 4 weeks. Similar results of improved attentional performance were found with citicoline administration in a study of healthy adult women (McGlade et al., 2012). Both of these studies found that with daily oral administration of citicoline, performance on the CPT-II increased. Specifically, adult women made fewer omission and commission errors and adolescent males had improved detectability and lower commission errors.

There are few known side effects following oral administration of uridine. Uridine is considered to be a safe dietary supplement with low risk for side effects and several potential benefits (e.g., increasing neuronal membrane synthesis) (Cansev, 2006). Further, there have been few reported adverse events even after administration of up to 300 mg a day of uridine for up to 20 years (Webster, 1995). The only noted side effects

with oral uridine administration include diarrhea and abdominal cramps (van Groeningen, Peters, & Pinedo, 1993).

Uridine as a Treatment for Depression in Bipolar Disorder

Uridine is also currently undergoing investigation as a treatment for depressed adolescents with BD. Uridine occurs naturally and is present in most human cells; it can also be found in tomatoes, broccoli, and mother's milk (Wurtman, 2008). Taken orally as a supplement, uridine is broken down in the stomach and specific uridine transporters facilitate circulation of uridine throughout the body (Cansev, 2006). Uridine is a pyrimidine nucleoside that is a critical element in the regulation of cellular energetics (Wurtman et al., 2010). Increasing the amount of uridine in the body may help facilitate the production of adenosine triphosphate (ATP) and increase brain pH (Jensen et al., 2008). An increase in brain pH has been shown to increase mitochondrial functioning, reduce glutamate and lactic acid levels, and increase phosphocreatine levels. There is evidence that pyrimidines are effective in the treatment of mitochondrial disorders, such as BD (Saydoff et al., 2013). Specifically, uridine and uridine prodrugs have successfully treated mitochondrial disorders (Jensen et al., 2008).

Triacetyluridine (TAU) is a uridine prodrug that is broken down into uridine after oral consumption. Naviaux (2000) investigated TAU in children with mitochondrial disorders and showed correction of renal tubular acidosis (RTA). Children with mitochondrial diseases were administered 2 grams of TAU three times daily for up to three years, and improvements in symptoms were noted (e.g., reduction in seizures, restoration of RTA) (Naviaux, McGowan, Barshop, Nyhan, & Haas, 1999). TAU has also shown to be effective in reducing symptoms of depression in adults. Jensen et al. (2008)

administered doses of up to 18 grams (6 gram doses 3 times daily) of TAU to 11 depressed adults with BD for 6 weeks and found that patients with a 50% decrease in depressive symptoms had a significant increase in brain pH from baseline.

Cytidine is another pyrimidine that is converted to uridine in the stomach. It has also has been investigated in the treatment of bipolar depression (Yoon et al., 2009). Results from a study by Yoon et al. administered placebo-controlled cytidine to 35 participants with BD in a depressive episode for 12 weeks. Participants in the study received one gram of cytidine or placebo twice daily combined with valproic acid. Individuals with bipolar disorder who received cytidine were shown to experience a significant reduction in depressive symptoms early during treatment compared to individuals who received placebo. Additionally, Yoon et al. showed that participants receiving the cytidine had a greater reduction in glutamate/glutamine levels than bipolar individuals taking placebo. Utilizing supplements that target the glutamatergic system has been proposed as an encouraging treatment for bipolar disorder. Studies of cytidine and uridine have suggested that they possess antidepressant-like properties (Carlezon et al., 2005; Carlezon et al., 2002) and Agarwal et al. (2010) suggested that uridine administration may be an effective treatment for individuals with BD.

Studies of uridine with healthy adults have also indicated that uridine treatment in BD may be beneficial. Agarwal et al. (2010) showed that 7 days of 2 grams of placebo-controlled uridine administration in 17 healthy adults increased total brain phosphomonoesters (PME). PME are necessary for the syntheses of phospholipid cellular membranes and are found in high concentrations in the developing brain (Bradler, Barrionuevo, Panchalingam, McKeag, & Pettegrew, 1991). It is important to note that individuals with BD have been shown to have decreased temporal lobe PME (Deicken,

Weiner, & Fein, 1995).

Kondo et al. (2011) administered 500 mg of uridine twice daily to 7 depressed adolescents with BD during a recent open-label trial of uridine. Kondo and his colleagues found a significant decrease in the adolescents' depression ratings after 6 weeks of treatment. Specifically, 7 depressed adolescents with BD demonstrated a 54% drop in depression ratings on the Children's Depression Rating Scale-Revised (CDRS-R).

Further, there is evidence that oral administration of uridine increases dopamine release (Wang, Pooler, Albrecht, & Wurtman, 2005). A 6-week animal study with 344 aged rats demonstrated that after supplementation with the 2.5% uridine additive found in infant formulas, there was a significantly greater release in striatal dopamine (DA) when compared to aged rats that consumed a controlled diet. Increasing dopamine in the brain may ultimately affect mood and cognition as decreased dopamine activity has been associated with depressive symptoms in mood disorders (Diehl & Gershon, 1992). Increased dopamine has shown to be associated with improved attention, working memory, and performance on cognitive tasks (Aalto, Bruck, Laine, Nagren, & Rinne, 2005). Therefore, uridine may benefit both mood symptoms and cognitive deficits in BD.

There are few treatments that address neuropsychological deficits in BD, and none have been designed especially for children. Previous research has examined the neurocognitive effects of lamotrigine treatment in pediatric BD (Pavuluri et al., 2010) and memantine administration with BD adults (Iosifescu, 2013). After lamotrigine treatment for 14 weeks, participants with BD showed significant improvement in symptoms of depression and mania. Working memory and verbal memory significantly improved with lamotrigine treatment, and participants with BD were no longer significantly impaired in these areas relative to controls. Executive function also significantly improved during

treatment, but participant performance still lagged behind controls at follow-up (Pavuluri et al., 2010). Placebo-controlled memantine was administered to 12 participants with BD in a euthymic state for 12 weeks, and there was significant improvement in working memory, visual, and verbal memory. Improvement of cognitive deficits in asymptomatic individuals with BD was associated with increased neuronal viability (NAA levels). A summary of neuropsychological deficits in youth with BD and the current treatments and symptoms they have addressed are summarized Table 1.

Purpose of the Study

Neuropsychological impairments are problematic for youth with BD. Deficits have been found in the domains of attention, executive functioning, memory, and processing speed (Horn, Roessner, & Holtmann, 2011). These deficits may greatly impact future social and vocational functioning for youth. Although current research has begun to acknowledge this issue, it is incompletely understood. Moreover, treatment for youth with BD typically entails the use of medications, some of which may further exacerbate neurocognitive problems. The current study was designed to contribute to the limited scientific literature regarding treatments to improve depressive symptoms and neurocognitive functioning in pediatric BD. The current study investigated the effects of uridine on depressive symptoms and neuropsychological functioning in youth with BD. It is the first study to examine the cognitive effects of uridine, a nonpharmacological intervention in youth with BD. Based on the neurocognitive deficits experienced by youth with BD, especially during a depressive episode, the following research questions were addressed in the current study.

Table 1. Treatments to Address Neuropsychological Deficits in Youth With BD

Domain	Types of Deficits	Treatments
Attention	Attention and vigilance Directing and sustaining attention	None
Executive Functioning	Switching attention to different stimuli (set shifting) Suppression of an action (response inhibition) Ability to switch thinking between multiple concepts (cognitive flexibility)	Lamotrigine significantly improved EF from baseline, but still lagged behind HC at follow-up (Pavuluri et al., 2010)
Working Memory	Working memory	Lamotrigine significantly improved WM (Pavuluri et al., 2010) Memantine significantly improved working and visual memory (Iosifescu, 2013)
Verbal Memory	Ability to encode and recall verbal information	Lamotrigine significantly improved verbal memory (Pavuluri et al., 2010) Memantine significantly improved verbal memory (Iosifescu, 2013)
Processing Speed	Ability to process visual information and perform motor tasks quickly	None

Research Questions

1. Are there significant differences in depressive symptoms after 6 weeks of placebo-controlled uridine administration between adolescents with BD taking uridine (N = 11) and those taking a placebo (N = 9)?
2. Are there significant differences in performance on neuropsychological tasks (e.g., memory, attention, etc.) after 6 weeks of placebo-controlled uridine administration between adolescents with BD taking uridine (N = 11) and those taking the placebo (N = 9)?
3. For adolescents with BD taking uridine, is there a quadratic effect of time on depressive symptoms?

Supplemental Research Questions

The following research questions were intended to examine differences between unaffected comparison participants (N = 10) and participants with BD (N = 20). Additionally, they were generated to further examine differences between adolescents with BD and unaffected comparison participants.

1. What are the differences in prestudy performance on neuropsychological tasks between nonaffected comparison subjects (N = 10) and depressed adolescents with BD (N = 20)?
2. What are the differences in prior educational experiences between unaffected comparison participants and adolescents with BD?
3. Is there a relationship between performance on neuropsychological tasks and academic difficulties for participants with BD?

CHAPTER II

METHODS

Participants

The present study was conducted concurrently with a placebo-controlled study of uridine administration at the University of Utah led by Douglas Kondo, Psychiatry Department faculty member in the School of Medicine. Kondo's double-blind randomized controlled trial was intended to investigate the effectiveness of uridine as a treatment for youth with BD during a depressed mood state. That study was approved by the Institutional Review Board (IRB) at the University of Utah on 3/27/2013 (IRB #00060256 and will be referred to as Study One). Study One was a larger study focused on investigating depressive symptoms and changes in glutamate and glutamine in depressed adolescents with BD after 6-weeks of placebo-controlled uridine administration observed with magnetic resonance spectroscopy (MRS) neuroimaging. Study One was responsible for randomization and administration of uridine.

The current study was a substudy of Study One to investigate both mood symptoms and neuropsychological performance during the placebo-controlled uridine trial. The current dissertation study was approved by the IRB on 4/28/2014 (IRB #00062904). Data used for the current analyses were drawn from both Kondo's Study One and from mood measures, neuropsychological testing, and academic information

Recruitment and Selection

Participants in Study One were invited to participate in the current dissertation study. Two groups of participants were recruited, one with BD who were currently in a state of depression and had been depressed for 2 weeks or longer, and a comparison group that did not have any evidence of BD or other psychiatric diagnosis (i.e., disorder found in DSM-IV) or medical condition. It should be noted that participants with BD in Study One were recruited using radio advertisements, informational flyers, posting in local news letters, posting on a local website, and advertisements on Trax. Flyers were posted in the community and given to local mental health providers and clinics. Mental health providers and local clinics left brochures and flyers in waiting rooms and distributed them to interested clients with BD. The brochures and flyers contained information about the study, eligibility requirements, and contact information.

Unaffected comparison (UC) participants were recruited for the current study in order to have age- and gender-matched controls for participants in Study One. Since studying adolescents with BD was the primary purpose of the current study, these participants were recruited first and began participation in the study. The unaffected comparison (UC) participants were recruited and began participation in the study procedures later. When the UC participants were initially recruited for Study One, flyers were placed around the local community. Recruitment for comparison participants was initially difficult because the UC participants received $125 compensation for participation in Study One, which included a diagnostic interview and a MRI brain scan. These participants were less interested in continuing in the current study, given the fact they were offered $25 for each study visit, for a total amount of $50. To increase participation in the current study, UC participants were scheduled for the baseline visit

of the current study the same day as the MRI scans for Study One.

Interested participants contacted this primary investigator (PI) of the current study and completed a phone screening prior to being scheduled for a screening visit. The phone screening involved providing information about the study to potential participants and asking questions to see if participants would meet the eligibility requirements and comply with study protocol. A total of 177 people contacted the PI and were interested in participating in the study; 125 of those were interested in participating in the bipolar disorder (BD) group and 52 were interested in participating in what was termed the unaffected comparison (UC) group. Thirty-eight potential participants were scheduled for a screening visit. Twenty-six potential bipolar participants were screened to determine study eligibility, and 21 of those subjects met eligibility criteria. Twelve unaffected comparison participants were screened to determine eligibility criteria, of which 10 were found eligible to participate in the study. Seven individuals did not meet the eligibility criteria, 5 were in the bipolar group and 2 were in the UC group. Figure 1 outlines the recruitment and selection of participants in the current study.

Participants with BD were males and females between the ages of 13 to 21 who were in a current depressive episode. All participants with BD met the DSM-IV-TR criteria for bipolar I, bipolar II, or bipolar-not otherwise specified (NOS) according to the SCID or the K-SADS. Dr. Kondo confirmed all diagnoses of BD and participant eligibility for Study One. Participants were required to be in Study One in order to be eligible to enroll in the current study. All bipolar disorders (bipolar I, II, or NOS) were grouped together into one bipolar group.

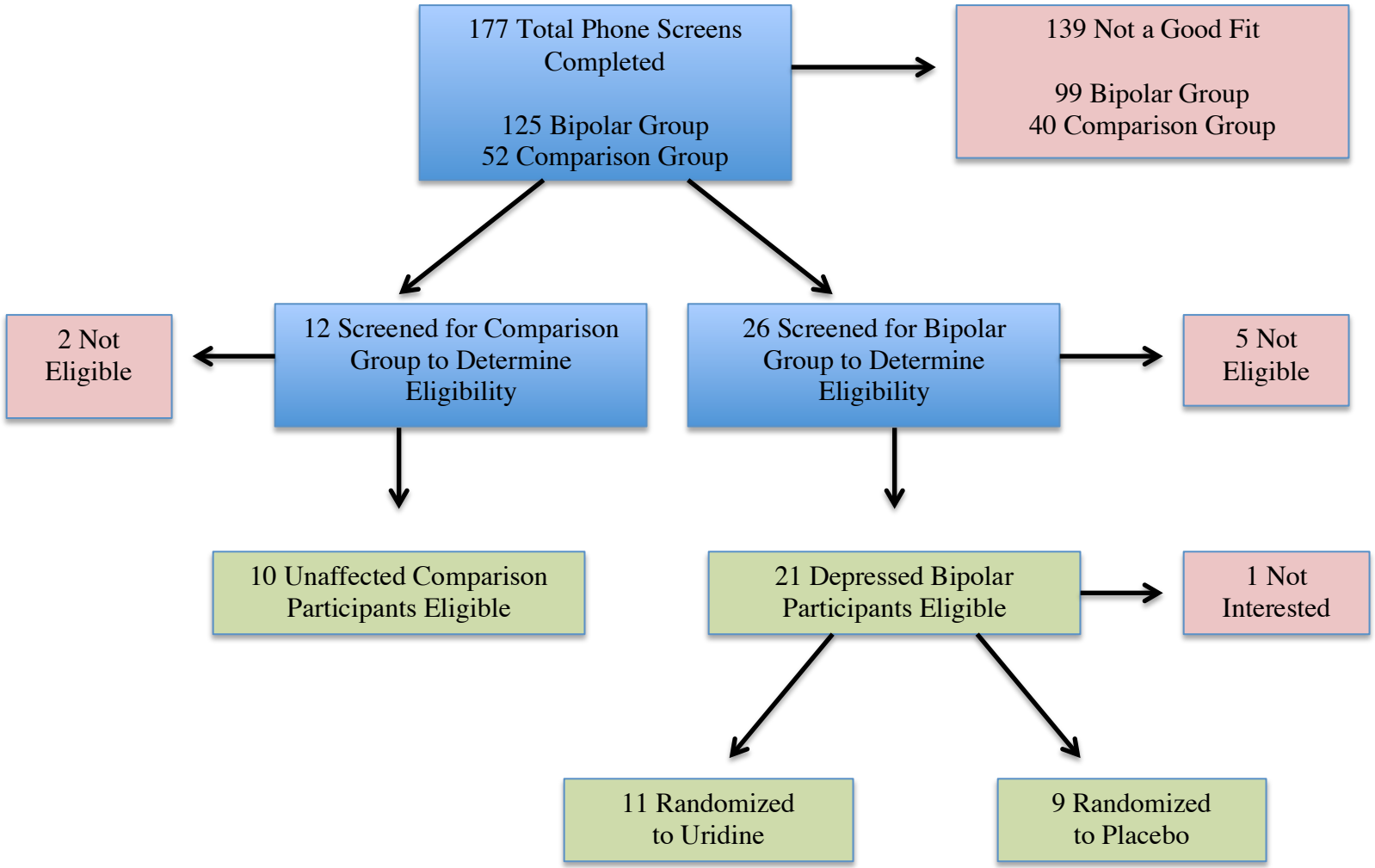

Figure 1. Recruitment and Selection of Participants.

Twenty-one participants with bipolar disorder consented to participate in the study. After consent was provided, 1 participant with BD withdrew from the study before attempting to complete any baseline measures given a lack of time or interest in participation. This participant, however, chose to stay enrolled in Study One. Of the 20 remaining participants with BD, 13 were female and 7 were male. The participants with BD ranged in age from 13 to 21.

An age- and gender-matched nonaffected comparison group was included in the study in order to provide a comparison to adolescents with bipolar disorder. Ten unaffected comparison participants completed the study. Participants in the comparison group had no current or previous diagnosed psychiatric disorder or substance use disorder as described in the DSM-IV-TR. Of the 10 unaffected comparison participants, 5 were male and 5 were female. Unaffected comparison participants ranged in age from 13-21. All participants had a standard score of 85 of higher on the Wechsler Abbreviated Scales of Intelligence-Second Edition (WASI-II; Wechsler, 2011). Exclusionary criteria used in the study included the following: 1) any comorbid medical, neurological, or psychiatric disorder that was not stable, or any current substance abuse; 2) participants who were in a manic mood state; 3) below- to low-average cognitive ability (i.e., FSIQ of 85 or below); 4) suicidal behaviors, homicidal behaviors, or self-harm behaviors; 5) positive urine drug screen for cocaine unless due to appropriate use of a medication prescribed to the participant; 6) known hypersensitivity to study drug or excipients; and 7) participants who in the opinion of the investigators (i.e., the current PI, the PI for Study One) were unlikely to comply with the study protocol. Figure 2 lists criteria required for study eligibility.

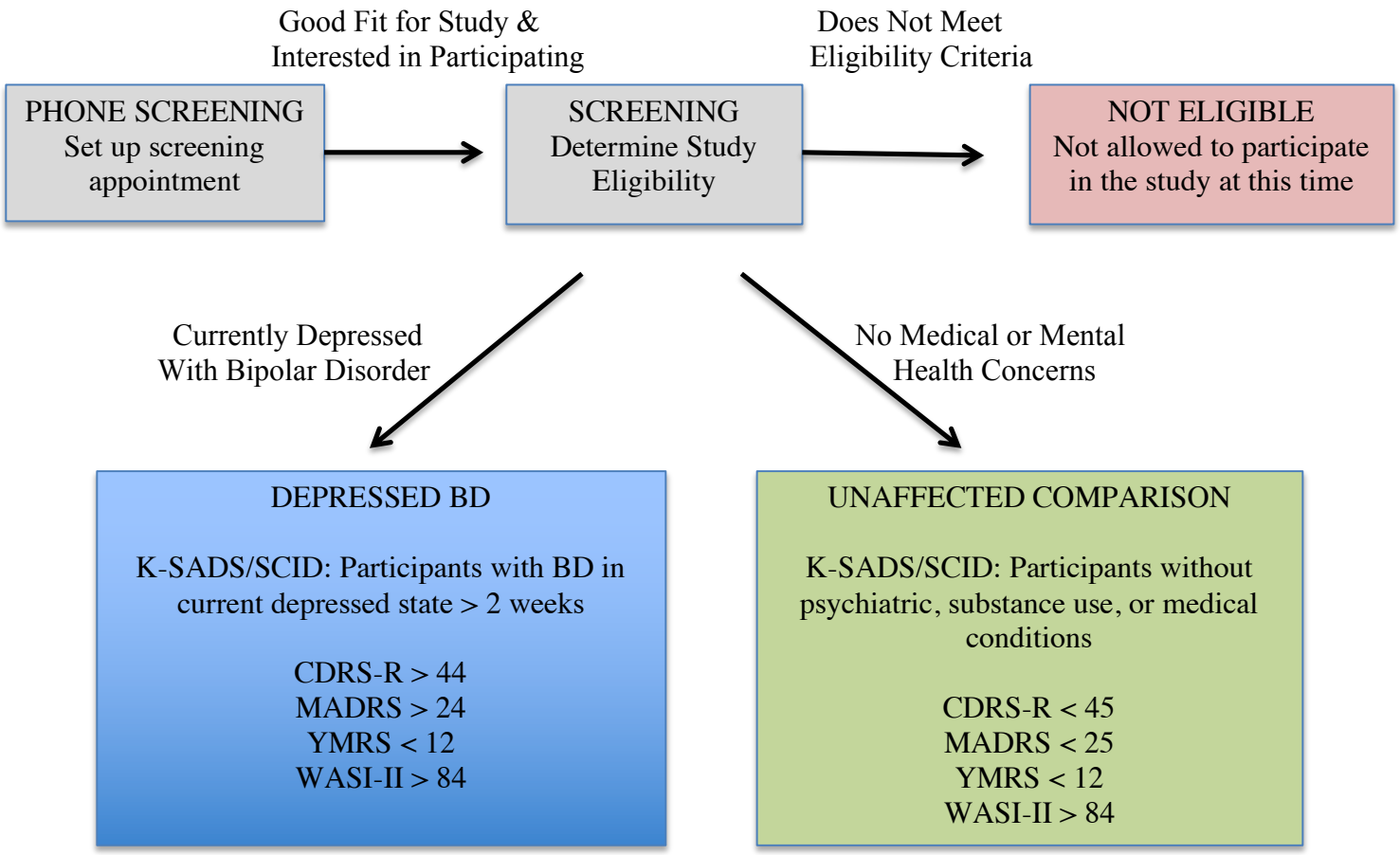

Figure 2. Eligibility Criteria to Participate in Study. K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia for School-age Children; SCID = Structured Clinical Interview for DSM-IV; CDRS-R = Children's Depression Rating Scale-Revised; MADRS = Montgomery-Asberg Depression Rating Scale; YMRS = Young Mania Rating Scale; WASI-II = Wechsler Abbreviated Scale of Intelligence-Second Edition.

Setting and Procedures

Interviews and assessment of study participants took place at the University Neuropsychiatric Institute (UNI). All tests were administered to participants individually. Data were collected over a 12-month period from 2014 to 2015. Parent(s) and the adolescent were provided with a description of the study and given time to ask questions and consider their participation in the study. At least 1 parent provided permission for their adolescent to participate in the study, and adolescents aged 13-17 provided informed assent, while individuals 18-21 years of age signed a consent form.

After providing permission, assent, or consent to participate in the study, all participants were screened for study eligibility. Specifically, the PI for the current study or a psychiatrist at the Brain Institute working on Study One administered the structured clinical interview, the *Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime* version (K-SADS-PL; Kaufman & Schweder, 2003). The K-SADS-PL was given to the parent(s) and all adolescent participants between the ages of 13 and 17. Participants who were 18 to 21 were directly administered the *Structured Clinical Interview for DSM-IV* (SCID I/P; First, Spitzer, Gibbon, & Williams, 1997).

The *Children's Depression Rating Scale-Revised* (CDRS-R; Poznanski & Mokros, 1996) and the *Montgomery-Asberg Depression Rating Scale* (MADRS; Montgomery & Asberg, 1979) were used to assess depressive symptoms. The *Young Mania Rating Scale* (YMRS; Young, Biggs, Ziegler, & Meyer, 1978) was also administered to assess symptoms of mania. The *Columbia Suicide Severity Rating Scale* (C-SSRS; Posner, 2010) was administered to participants to assess suicidal ideation and self-harm. The *Wechsler Abbreviated Scale of Intelligence-Second Edition* (WASI-II; Wechsler, 2011) two-subtest version (Vocabulary and Matrix Reasoning) was

administered to all participants to determine if they had a score within the normal range. An ECG, blood, and urine samples from each participant were completed on each participant with BD by the principal investigator. Dr. Kondo obtained medical histories and conducted a physical exam.

Once the adolescents with BD were determined to be eligible for study participation, they were randomly assigned to receive a placebo or 500 mg of uridine twice daily for 6 weeks. All participants with BD returned for weekly study visits and complete mood measures to ensure that they did not experience mood shifting throughout the study. After 6 weeks of placebo-controlled uridine administration, participants came back for a follow-up visit 2 weeks later. Unaffected comparison participants were not administered placebo-controlled uridine; however, they remained in the study for 6 weeks and completed mood and neuropsychological measures at baseline and final visits.

Eligible participants completed neuropsychological measures and mood measures (described below) at the baseline and final study visits. Figure 3 diagrams the study procedures for all participants. The baseline study measures occurred within 1 week of the screening visit and prior to the placebo or the uridine administration. The final study visit was conducted approximately 6 weeks after the baseline study visit, prior to participants ending treatment with placebo or uridine. All participants completed all tests measures. At each weekly study visit, vital signs and information regarding side effects of placebo-controlled uridine, adverse events and concomitant medications were collected. Study staff also checked participants' weekly logs (see treatment integrity section) for treatment adherence and recorded any missed doses of placebo-controlled uridine. Mood measures were administered at weekly visits to monitor mood. The final study occurred within 1 week of completing placebo-controlled uridine administration.

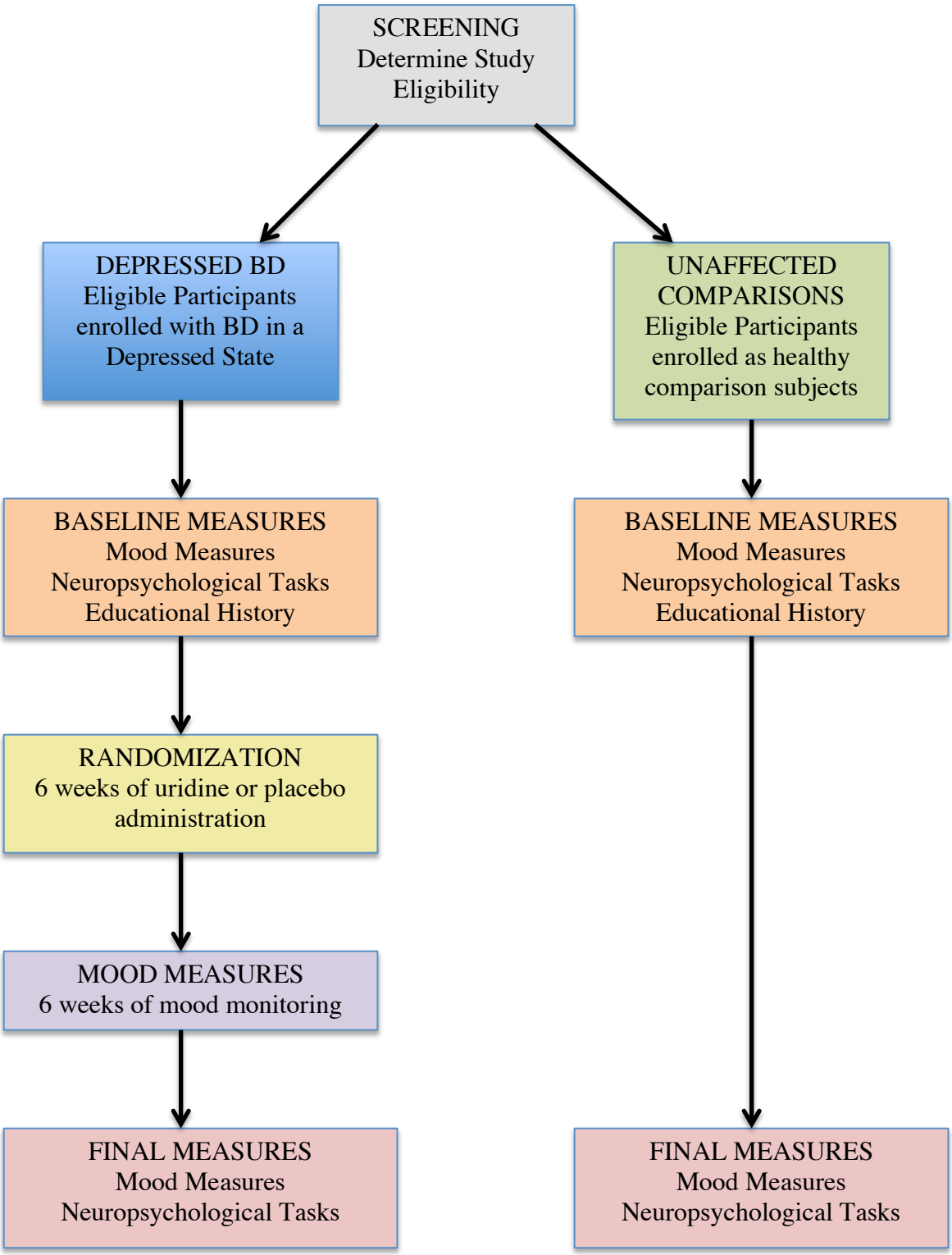

Figure 3. Study Procedures for All Participants.

Participants with BD who completed all study procedures were compensated a total of $290. As previously described, for participating in Study One, they were paid $240 for completing screening, weekly study visits, follow-up, and two MRI scans. For the current study, participants were paid an additional $50, with $25 paid for completing the baseline study measures and $25 for completing the final study measures.

Participants were assigned an alphanumeric study identification number to which all data in the study were linked. All personal identifiers were removed from the data in the analyses. The data were stored in a locked closet at a secure location at the Brain Institute at the University of Utah. This is the location of the office of the primary investigator of the larger study, or Study One.

The PI for the current study along with Dr. Kondo (the PI for Study One) administered all measures according to standardized procedures. During the assessments, participants were observed for signs of fatigue or distress and were offered opportunities for breaks. Scoring of all protocols and entering data into a secured database were completed by the Principal Investigator.

Instruments

Participants completed psychiatric and mood measures to determine eligibility for the current study (see Table 2). Specifically, participants completed a diagnostic interview and depression, mania, and suicide rating scales, which took about 90 to 120 minutes to administer. Additionally, at the baseline visit, participants completed the *Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II)* two-subtest version (Vocabulary and Matrix Reasoning subtests), which took about 15 minutes to administer.

Table 2. Measures for Study Eligibility

Domain	Measures	Age Range
Clinical Interview	*Kiddie Schedule for Affective Disorders and Schizophrenia for School-age Children, Present and Lifetime Version (K-SADS-PL)*	13-17
	Structured Clinical Interview for DSM-IV, Research Version, Patient Edition (SCID I/P)	18-21
Cognitive Ability	*Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II)*	13-21
Depression	*The Children's Depression Rating Scale-Revised (CDRS-R)*	13-18
	Montgomery-Asberg Depression Rating Scale (MADRS)	19-21
Mania	*Young Mania Rating Scale (YMRS)*	13-21
Suicidal Ideation/ Behavior	*Columbia Suicide Severity Rating Scale (C-SSRS) Baseline Version*	13-21

Measures for Study Eligibility

Clinical Interview

The *Kiddie Schedule for Affective Disorders and Schizophrenia for School-age Children, Present and Lifetime* version (K-SADS-PL; Kaufman & Schweder, 2003) is a structured clinical interview that assesses the current and lifetime presence and severity of psychopathology in children according to DSM-IV criteria. Consisting of 82 items and 5 supplemental sections, it is administered to at least 1 parent and youth ages 13-17.

The K-SADS-PL requires completion of an introductory interview, diagnostic screening interview, and appropriate diagnostic supplements based on endorsement of current or past psychopathology. Information is gathered and summarized from all sources and current and lifetime ratings are made for each diagnosis. Symptoms are coded as not present, subthreshold, threshold, or no information. The K-SADS-PL has shown concurrent validity and test-retest reliability kappa coefficients in the excellent range (.77-1.0) for present and lifetime diagnoses of MDD, BD, anxiety disorder, conduct disorder, and oppositional defiant disorder (Ambrosini, 2000; Kaufman et al., 1997). Additionally, the K-SADS-PL has high sensitivity in diagnosing patients with BD. Each adolescent participant between the ages 13 and 17 and 1 of their parents completed the K-SADS-PL with the PI's (Huber and Kondo) to provide comprehensive information regarding current/past symptoms, medical/treatment history, family/school information, and current level of functioning.

The *Structured Clinical Interview for DSM-IV* (SCID I/P; First et al., 1997) is a semistructured diagnostic interview used to assess current and past symptoms of psychopathology in individuals 18 and older. The SCID is the most frequently used semi-structured interview in clinical research used to diagnose mental disorders included within the DSM-IV, including mood, anxiety, psychotic, substance use, somatoform, and adjustment disorders. There is an overview and screening questions for each module of the SCID. Sections of the SCID corresponding to diagnoses are skipped or completed based on answers to screening and entry questions in each section. All symptoms are rated as present, subthreshold, or absent for each disorder. Raters who have received appropriate training in administering the SCID have demonstrated a high level of test-rest reliability and accuracy in diagnosis (e.g., kappas of at least .75 on symptoms and 90%

accuracy in diagnosis) (Ventura, Liberman, Green, Shaner, & Mintz, 1998). The SCID was administered to participants between the ages of 18 and 21 by the PI to provide comprehensive information regarding current/past symptoms, medical/treatment history, family/school information, and current level of functioning.

Cognitive Ability

The *Wechsler Abbreviated Scale of Intelligence-Second Edition* (WASI-II; Wechsler, 2011) is a brief measure of cognitive ability that can be administered to individuals between the ages of 6 and 90. It consists of four subtests: Vocabulary, Similarities, Block Design, and Matrix Reasoning. Both the four-subtest version and two-subtest version may be used to obtain a Full Scale IQ (FSIQ). When the four-subtest version is administered, a Verbal Comprehension Index (VCI) and a Perceptual Reasoning Index (PRI) are obtained. This version takes about 30 minutes to administer. The Vocabulary and Matrix Reasoning subtests can be combined to form the Full-Scale IQ-2 Subtests (FSIQ-2). The two-subtest version takes approximately 15 minutes to administer and provides an adequate estimate of general ability (Wechsler, 2011). The WASI-II has excellent internal consistency, test-retest stability and concurrent validity with the WISC-IV and WAIS-IV (McCrimmon & Smith, 2013). All participants were administered the two-subtest version of the WASI-II to confirm that their cognitive ability fell within the average- to above-average ranges (i.e., FSIQ of 85 or above).

Depression

The *Children's Depression Rating Scale-Revised* (CDRS-R; Poznanski & Mokros, 1996) is a clinician-completed semistructured interview to assess depression in

17 symptom areas, including those found in the DSM-IV. The CDRS-R takes about 20 minutes to administer, and information about the child's level of depression can also be obtained from parents and teachers. Each item is rated on a scale from 1 to 5, or 1 to 7. The lowest score (1) is for "no difficulties" and the highest score (5) or (7) is for "severe clinically significant difficulties." All items are summed together for a total score, which is converted into a *T*-score. Interpretation is based on the range in which *T*-scores fall. For example, if a child obtains a *T*-score in the 65-74 range, a depressive disorder is "likely to be confirmed upon further questioning." Interrater reliability for the CDRS-R was .74 for those familiar with it and .75 for those unfamiliar with it (Dowd, 2001). Item-total correlations for interviewers familiar with the CDRS-R had a median of .62, whereas those unfamiliar with it had a median of .61. Test-retest reliability after 2 weeks was .80 (Stovall, 2001). Frazier et al. (2007) evaluated the factor structure of the CDRS-R and found two separate factors, cognitive and somatic/affective symptoms. The CDRS-R has been validated for use in child populations, but it has also been widely used in adolescent populations ages 13-17 years of age as a measure of depression for clinical trials. The CDRS-R was administered to all participants by the PI and Dr. Kondo to assess depressive symptoms throughout the study.

The *Montgomery-Asberg Depression Rating Scale* (MADRS; Montgomery & Asberg, 1979) is a 10-item clinician-administered rating scale for assessing the core symptoms and cognitive features of depression, which takes about 15 minutes to administer. Each item is rated on a scale from 0 to 6, with anchor points at ratings of 0, 2, 4, and 6. All ratings on the MADRS are summed to generate a total score. Higher scores on the MADRS indicate an increase in the severity of depression. A score of 31 is considered "severe," while 7 and under is considered "not depressed." The MADRS has

high internal consistency, $r = .95$ (Galinowski & Lehert, 1995) and good interrater reliability, ranging from .89 to .97 (Montgomery & Asberg, 1979). The MADRS has been shown to be a valid instrument and to have high correlations ($r = .90$) with other depression rating scales such as the *Hamilton Depression Rating Scale* (Muller, Himmerich, Kienzle, & Szegedi, 2003). The MADRS was administered to all participants to assess depressive symptoms at baseline and at every study visit. The MADRS is typically used with adults 18 years and older, and since there were participants ages 18-21 years old in the study, both the MADRS and CDRS-R were given to all participants to increase the reliability in depression ratings.

Mania

The *Young Mania Rating Scale* (YMRS; Young et al., 1978) is a clinician-administered interview to assess symptoms of mania which takes about 20 minutes to administer. The YMRS is one of the most frequently used measures to assess symptoms of mania in youth and adults. It consists of 11 items and is based upon the individual's report of symptoms in the past 48 hours and the interviewer's behavioral observations. Each item has five levels of severity and the items are summed together for a total score. The YMRS total score may range from 0 to 60 and a score of 12 or less typically is characteristic of no symptoms of mania. The YMRS has excellent interrater reliability, ($r = .93$) and concurrent validity between the total score and independent global ratings (Young et al., 1978). The total YMRS score was also shown to have a high correlation with the number of days that patients were hospitalized. The YMRS was administered to all participants to assess symptoms of mania at baseline and throughout the study.

Suicidal Ideation/Behavior

The *Columbia Suicide Severity Rating Scale* (C-SSRS; Posner, 2010) is a clinician interview to assess recent and lifetime symptoms of suicidal ideation and self-harm behavior in participants. When administering the C-SSRS, the intensity of any suicidal ideation (e.g., frequency, duration, controllability, etc.) is rated. Any reported suicidal behavior is also recorded, including the total number of attempts (aborted or interrupted) and any preparatory acts or behavior. For actual attempts, the lethality is rated. Posner et al. (2011) found that the C-SSRS has high sensitivity and specificity for suicidal behavior, and that the ideation and behavior subscales are sensitive to change over time. The C-SSRS has also shown strong convergent validity with other established suicidal ideation and behavior rating scales (e.g., Scale for Suicide Ideation, Suicidal Ideation Questionnaire-Junior). In a study with adolescents, the C-SSRS successfully predicted suicide attempts during the study (Posner et al., 2011). The C-SSRS Baseline version assesses most severe suicidality over the lifetime and current suicidality and was administered to all participants at the baseline. The C-SSRS Last Visit version was administered to all participants at each subsequent visit following the baseline visit to assess for changes in suicidal ideation or behavior. The risk of suicide in participants with BD was closely monitored during the study using the C-SSRS. No participants were withdrawn from the study due to an increase in suicidal ideation or behavior.

Study Measures

Mood Assessments

The mood measures (described above) were administered to all participants at the screening visit and then used at each subsequent study visit to monitor mood symptoms

and mood episodes. No participants with BD switched to a manic episode during the study, and all scores on the YMRS were below 12. Additionally, mood symptoms for any of the participants with BD did not worsen to a point that the PI felt that a participant was unsafe or that he or she needed to be withdrawn from the study.

Neuropsychological Assessments

The neuropsychological tests assessed the following domains: 1) attention, 2) executive function, 3) working memory, and 4) verbal memory. The measures selected in these domains are widely used in both clinical and research settings and have been used in previous studies to assess neurocognitive functioning in youth with BD. These instruments were selected to collectively measure these domains of neuropsychological functioning, due to their good specificity in clinical and comparison groups and their high sensitivity in detecting changes from treatment. Neuropsychological tests listed in Table 3, which took about 90 minutes to administer, were given to all participants on the first and final study visits.

Attention. The *Conners Continuous Performance Test-Second Edition* (CPT-II; Conners, 2005; Deicken et al., 1995) is a computer-based program that measures attentiveness, impulsivity, sustained attention, and vigilance. On the CPT-II, participants respond to visual stimuli on the computer screen for varied presentation rates and intervals. Participants press the space bar whenever any letter other than the letter "X" appears on the screen. Instructions and a practice session are given before the CPT-II begins. The CPT-II displays letters for 250 milliseconds at 1-, 2-, and 4- second intervals for approximately 15 minutes. The CPT-II has shown good split-half reliability and validity, has been found to discriminate between clinical and nonclinical

Table 3. Study Measures.

Domain	Measure
MOOD ASSESSMENTS	
Depression	*The Children's Depression Rating Scale-Revised (CDRS-R)* *Montgomery-Asberg Depression Rating Scale (MADRS)*
Mania	*Young Mania Rating Scale (YMRS)*
Suicidal Ideation/ Behavior	*Columbia Suicide Severity Rating Scale (C-SSRS)*
NEUROPSYCHOLOGICAL ASSESSMENTS	
Attention	*Conner's Continuous Performance Test (CPT-II)*
Executive Functioning	*Wisconsin Card Sorting Test - Computer Version 4 (WCST)* *D-KEFS Trails Making Test (Condition 4)* *D-KEFS Color-Word Interference Test (CWIT)*
Working Memory	*Wechsler Intelligence Scale - 4th ed. (WAIS-IV)* Working Memory Composite
Verbal Memory	*California Verbal Learning Test – 2nd ed. (CVLT-II)*
Processing Speed	*Wechsler Intelligence Scale - 4th ed. (WAIS-IV)* Processing Speed Composite
ACADEMIC PERFORMANCE	
Academic	*Academic Performance Rating Scale (APRS) - teacher* *Behavior Assessment System for Children, 2nd ed. (BASC-2)*

youth, and is sensitive to medication changes in treatment (Riccio, Waldrop, Reynolds, & Lowe, 2001). All participants were administered the CPT-II at the baseline and final study visits. The variables of interest on the CPT-II were detectability, omission errors, commission errors, and variability. Detectability provides information on how well the examinee discriminates between targets and nontargets. Greater overall errors of detectability may indicate problems with accuracy and attention. Errors of omission indicate failure to respond to a target item and a high number might indicate distractibility. Commission errors are responses to nontarget items, and a high number may indicate impulsivity. Variability measures consistency of time in responding to targets over the length of the test.

Executive functioning. The measures of EF were selected based on Banich's (2009) integrative theory that neurobiological, psychological, and computation levels of the brain are all involved in executive processes. This model takes previous theories of EF into account and focuses on executive processes involved in updating, set-shifting, and inhibition. Assessments that were selected to measure these processes are widely used in both clinical and research settings, and have been used in previous studies assessing neurocognitive functioning in youth with BD and depressed youth. These instruments were selected as measures of EF due to their high sensitivity and specificity between clinical and comparison groups (Weyandt et al., 2012).

The *Wisconsin Card Sorting Test* (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993) is a measure of executive functioning used to assess abstract concept formation and cognitive set-shifting that can be administered by an examiner or on the computer. In the WCST, participants are asked to categorize cards to one of four stimulus cards placed in front of them. The stimulus cards consist of various geometric forms that

have different shapes, colors, and numbers. The participant is given one card at a time and asked to sort it according to an underlying principle. The participant's task is to learn the sorting rule. After each sorting attempt, the examiner provides corrective feedback so the participant may deduce the sorting principle. Once the criterion level of successful performance has been reached with a particular rule, the sorting rule changes and the participant must then decipher the new sorting principle. The sequence continues until all of the 128 cards are sorted, or six runs of 10 consecutive responses according to the correct principle are completed.

The WCST has been normed with children and adolescents and can be used with individuals aged 6 ½ to 89. The total number of errors, perseveration errors, and conceptual responses are recorded. Perseveration errors are the number of times that a participant responds according to a particular principle, despite being informed that the principle is incorrect. Conceptual responses are correct responses that occur in sequences of three or more. Interscorer reliability of the WCST ranges from .83 to 1.00. In a sample of children and adolescents, the standard error of measurement ranged from 7.94 to 11.91 (Heaton, 1993). The WCST Computer Version 4-Research Edition was administered on the computer to all participants at baseline and final study visits.

Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test, Number-Letter Switching Condition (D-KEFS; Delis, Kaplan, & Kramer, 2001) is an assessment of cognitive set-shifting. In the D-KEFS Trails Number-Letter Switching Condition, participants draw a line to connect circles with numbers and letters in an alternating fashion. Instructions are provided and each participant must successfully complete the sample item to demonstrate understanding before beginning the task. The D-KEFS Trails Number-Letter Switching Condition consists of 25 numbers and letters (numbers 1 to 13

and letters A to L) in circles on two adjacent pages. The participant is asked to connect the circles by alternating between numbers and letters in order as quickly as possible. The score is the time required in seconds to complete each trial and the number of errors made. The D-KEFS Trails Number-Letter Switching Condition was administered to all participants at the baseline and final study visits.

D-KEFS Color-Word Interference Test (CWIT) (D-KEFS; Delis, Kaplan, & Kramer, 2001) is a measure of executive functioning that assesses inhibition. The CWIT takes about 5 minutes to administer and can be used with individuals aged 5 to 90. For the CWIT, participants are presented three traditional Stroop trials (color naming, color name reading, interference) and a fourth trial in which the participant switches between naming the color of ink and the conflicting color names. In the first trial of word reading, the participant is asked to read the names of color (e.g., red, blue) displayed in black ink. Participants are asked to read down each column and say the color name aloud. During the color trial, participants identify colors alone (rectangles printed in red, blue, or green). During the interference trial, participants are presented with the names of colors, which are printed in a differ color, and are asked to say the color of the ink the words are printed in rather than reading the color-words. The switching interference trial requires the participant to say the color of ink the color-words are printed in as in the previous interference trial, but if a word is in a box, the participant has to read the word and not say the color of ink. This requires the participant to switch between naming the color of the ink and the conflicting color names. After each response, the experimenter determines the accuracy of the participant's response. Each trial produces a score, based on the number of uncorrected and self-corrected errors and the total amount of time to complete each trial. Test-retest reliability scores range from .62 -.76 and the split-half reliability

ranges from.62-.86, with both types of reliability being moderate to high (Delis et al., 2001). The CWIT was administered to all participants at the baseline and final study visits.

Working memory. The Digit Span and Letter-Number Sequencing subtests from the *Wechsler Adult Intelligence Scale – 4th Edition* (WAIS-IV; Wechsler, 2008) were administered to all participants in the study to assess working memory. The WAIS-IV was used with all participants in the study without regard for the age limitation of this test (age 16 and up). The Digit Span subtest requires the participant to repeat numbers forward or backwards in the same order as read aloud by the examiner, or mentally arrange numbers in ascending order as read aloud by the examiner. The Letter-Number Sequencing subtest requires the participant to mentally arrange numbers in ascending order and letters in alphabetical order as read aloud by the examiner. Internal consistency of the WAIS-IV Working Memory Index was .94 (Wechsler, 2008b). Test-retest stability of the Working Memory Index for the WAIS-IV was .87, with an average of 3 weeks between testing.

Verbal memory. The *California Verbal Learning Test – Second Edition* (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) was administered to all participants to assess verbal learning and memory at the baseline and final study visits. The CVLT-II is a word-list learning task in which 16 words from List A are presented over five learning trials. Words are presented orally at the rate of one word per second and at the end of each trial, participants are asked to recall as many words from List A as possible. An interference word List B is given as a distractor, and then participants are asked to recall words from List A. Participants are cued with categories for the words (e.g., clothing, fruit, etc.) and are asked to recall as many words as they can in each category. After a 20-minute delay,

participants are asked to recall as many words from List A as possible. The final task is a recognition trial that presents words from List A with 16 distractor items. Participants have to make a forced choice (yes or no) if each word was in List A when asked. Scoring the CVLT-II includes the total number of words recalled during trials 1-5, the number of words recalled on delayed recall of List A, and recognition. These scores are converted into standardized scores. There is high test-retest reliability for immediate, delayed, and recognition trials of the CVLT-II (Delis et al., 2000).

Processing speed. The Symbol Search and Coding subtests from the *Wechsler Adult Intelligence Scale – 4th Edition* (WAIS-IV; Wechsler, 2008) were administered to all participants to assess processing speed. The Symbol Search subtest requires the participant to visually scan a group of symbols and mark whether or not one of the symbols in the target group matches. The Coding subtest requires the participant to use a key and copy symbols that are paired with numbers within a specified time limit. Participants are allotted 2 minutes for each subtest. The total raw scores of the Processing Speed Index were computed and used in the analyses. Average test-rest reliabilities of the WAIS-IV Symbol Search and Coding were .80 and .83 (Wechsler, 2008b). Internal consistency of the Processing Speed Index for the WAIS-IV was .90, and test-retest stability was .84.

Academic Measures

The *Academic Performance Rating Scale* (APRS; DuPaul & Rapport, 1991) is a rating scale for teachers to rate student academic skills and performance in the classroom within the past week. Higher scores indicate greater academic performance and success. The rating scale consists of 19 items on a 5-point scale. A principal components analysis

(PCA) revealed three factors for the APRS: academic success, impulse control, and academic productivity. The total APRS had adequate internal consistency (.95), as did the Academic Success (.94) and Academic Productivity (.94) subscales. The test-retest reliability was high for the total APRS (.95) and for Academic Success (.91) and Academic Productivity (.93) subscales for a 2-week period (DuPaul & Rapport, 1991). The APRS was completed by the teachers of 2 participants with BD in the current study.

The *Behavior Assessment System for Children, Second Edition* (BASC-2; Reynolds & Kamphaus, 2006) uses teacher report to measure school performance/problems at baseline and posttreatment. The BASC-2 teacher report includes 100 items that are rated on a 4-point scale of frequency of occurrence. There are numerous composites and subscales on the BASC-2, but the subscales of interest for the current study were School Problems, Learning Problems, and Study Skills. For the clinical scales (School Problems, Learning Problems), *T*-scores of below 60 are considered normal, while scores from 60-69 are at-risk, and scores above 70 are clinically significant. For the adaptive scales (Study Skills), *T*-scores of 41-59 are average, 31-40 are at-risk, and scores 30 and below are considered clinically significant. Internal consistency of composite scores has been shown to be adequate (.90), while subscale scores across teacher, parent, and student forms have internal consistencies of .80. Test-retest reliability of composites on the BASC-2 is .80, while subscale reliability ranges between .70 to .80 (Reynolds & Kamphaus, 2006). The BASC-2 was completed by the teachers of 2 participants with BD.

Eleven subjects with BD and 3 comparison participants were on summer break from school during participation in the study and were unable to have academic performance rated by teachers. Additionally, 3 participants with BD and 3 comparison

participants were not students during the study because they had completed or discontinued an academic program and therefore, did not complete academic performance ratings. Two participants chose not to have teachers rate their academic performance. Two participants with BD and 1 comparison participant did not return the academic measures. There were 2 participants with BD and 3 comparison participants that completed measures of academic performance at the baseline and final study visits. These participants were both in the uridine group. Academic performance measures were intended to evaluate academic performance and functioning for all participants in the study. Since these measures were only completed by 2 participants in the same BD group, they were not used in the final analyses. Each of the 2 participant's teachers completed two measures that provided information about the participant's academic performance and functioning.

Interrater Reliability

The principal investigator was trained on all mood, neuropsychological, and academic measures. For reliability purposes, the principal investigator and Dr. Kondo completed all diagnostic interviews and mood rating scales. Thirty-three percent of interviews and mood rating scales were randomly selected and rated by both Dr. Kondo and the principal investigator. Interrater reliability was calculated to determine consistency among raters for the K-SADS/SCID, CDRS-R, MADRS, and YMRS using Cohen's kappa. According to kappa ratings by Landis and Koch (1977), each measure was found to have substantial (K = .61 to .80) or almost perfect agreement (K = .81 to .99). The interrater reliability for diagnostic interviews was found to have almost perfect agreement, K = .93, p < .001. Depression ratings were found to have substantial

agreement CDRS-R, $K = .751$, $p < .001$, and MADRS, $K = .73$, $p < .001$. Additionally, interrater agreement on the YMRS was found to have substantial agreement, $K = .66$, $p < .001$. Only the principal investigator administered and scored the neuropsychological tasks and the academic performance checklists.

Treatment Integrity

Participants' adherence to treatment was measured throughout the study. At each weekly study visit, participants were given a supply of placebo-controlled uridine. Participants were given a weekly log to write the time of day (morning and night) that they took the placebo-controlled uridine and had a parent initial at that time. If participants did not live with a parent, they initialed for themselves. Participants brought their logs to each weekly study visit and discussed any missed doses. If participants did not remember to bring logs or study medication to a weekly visit, they were asked to bring it to the next consecutive visit. Logs were discussed at each visit and leftover study medication was counted at each visit. Any missed study medication doses and the amount of study medication returned at each visit were noted on a master log for each participant. Two participants did not return logs or left over study medication throughout the study, but their parent confirmed that study medication was taken each day and that no doses of study medication were missed.

Treatment adherence was calculated for each participant, and it was found that 3 participants missed more than the 10% established cut-off amount of placebo-controlled uridine doses throughout the study. These participants were considered non-adherent and were not included in the data analyses. All missed doses were discussed with participants and their parents. Participants were asked to set a reminder to take all study medication.

One participant taking the placebo missed one dose of study medication during the 2nd and 5th weeks of the study. During the 3rd and 4th week of the study, the participant did not miss any doses of study medication. The final week of the study, the participant brought back all but one day of study medication for that week, which indicated that participant missed 6 doses of study medication that week. The participant missed a total of 8 doses of study medication throughout the study.

One participant taking uridine did not bring back their log or any left over study medication throughout the study. At the week 6 visit, the participant brought back 48 capsules of study medication and had missed 7 days of study medication. Another participant taking uridine reported missing approximately 1 dose of uridine each week. This participant was asked to set an electronic reminder to take the study medication. Additionally, this participant brought back all left over study medication at week 6 and stated that they had missed 2 doses that week. Over the course of the study, the participant had missed a total of 10 days of study medication.

During the study, 2 participants missed one weekly study visit. One of the participants started a new job and forgot to attend the week 4 visit, despite reminder text/phone calls. The other participant went on a camping trip to a remote location without cell phone service, and even though a phone visit was offered that week, the week 3 visit was not possible. All participants were able to attend appointments either in person or by phone when an in-person visit was not possible. There were not any participants who missed 2 consecutive weekly study visits during the study or were removed from the study due to noncompliance. Therefore, all but 3 of the 30 total participants were included in the data analyses.

Design

The current study utilized 2 x 2 mixed factorial designs that used both between-group and repeated measures to compare mean differences of composites for BD participants who received uridine to those who received placebo pre- and posttreatment. The between-group variable was the treatment that participants with BD were randomized and administered (uridine vs. placebo). The repeated measures variables were the measurement of mood symptoms and neuropsychological performance over time (pretreatment vs. posttreatment). The larger study from which the data for this study were drawn represented a repeated measures design. In that study, mood was measured weekly for participants with BD who had been administered placebo-controlled uridine. To answer the third research question, data were graphed utilizing scatter plots and tested for a quadratic effect of time on mood symptoms for the participants with BD taking uridine.

The first supplemental research question utilized between-subjects analysis of variance (ANOVA) to compare baseline neuropsychological performance of participants with BD to unaffected comparison participants. Academic and educational histories of bipolar and unaffected comparison participants were summarized and Fisher's exact test of independence was used to analyze educational experiences of both groups in the second supplemental question. Since participants were on break from school, and some participants did not attend school, questionnaires were not completed by a teacher. The third supplemental question utilized bivariate correlations to examine each academic difficulty experienced and difference in performance on neuropsychological composites.

Data Analyses

Descriptive statistics were calculated for all demographic and clinical variables using means and standard deviations for each sample. Participant performance on individual measures was described by calculating the total raw score for each variable and standardizing (i.e., converting to z-scores) both baseline and posttreatment scores relative to performance of the unaffected comparison participants' performance on each assessment variable at baseline. Expressing all scores in the same units facilitated comparisons of variables across occasions, and the combination of similar variables to form composites.

All variables were checked for normality, including skew, kurtosis, and homogeneity of variance. Outliers were defined as scores that were greater than 3 z-scores. In cases where outliers were detected, the individual data point was examined first to verify that it did not result from a data error and represented a valid case. For outliers deemed to be valid, the data point was retained, but the score was converted to +/- 3.0 to decrease its influence (Tabachnick & Fidell, 2007).

Since there were a smaller number of subjects than expected, it was not possible to use factor analysis to form composites. Using standardized scores, composites were formed for each of the domains based on theory from previous studies, and correlation between the variables as evidenced by a correlation matrix. All variables combined into composites had correlations > .4.

Composites were formed by adding or subtracting the standardized variables and dividing by the total number of variables combined together for the following domains: depression, attention, memory, verbal memory, executive functioning, and processing speed. Using the five neuropsychological composites, a global neuropsychological

composite score was created by averaging the five composites together. Correlations of baseline composites are displayed in Table 4.

The depression composite was comprised of the total score for the *Children's Depression Rating Scale (CDRS)* and the total score for the *Montgomery-Asberg Depression Rating Scale (MADRS)*. The neuropsychological domain composites were constructed as follows: Attention composite based on the *Conners Continuous Performance Test-Third Edition (CPT-3)*; Executive Function composite based on the *Wisconsin Card Sorting Test (WCST), Delis-Kaplan Executive Function System D-KEFS* Trails, and Color Word Interference Test; Working Memory composite based on the *Wechsler Adult Intelligence Scale-4th Edition (WAIS-IV)* Working Memory Index; Verbal Memory composite based on scores from the *California Verbal Learning Test-Second*

Table 4. Correlation Matrix for Baseline Composites.

Composite	Depression	Attention	Memory	Executive Function	Verbal Memory	Processing Speed
Depression	--					
Attention	-.121	--				
Memory	-.392	.502*	--			
Executive Function	-.378	.641**	.648**	--		
Verbal Memory	-.284	.374	.460*	.481*	--	
Processing Speed	-.214	.493*	.777**	.671*	.334	--

**$p < .01$, **$p < .05$

Edition (CVLT-II); and Processing Speed composite based on the *Wechsler Adult Intelligence Scale-4th Edition (WAIS-IV)* Processing Speed Index. See Table 5 for the domains, measures, and the variables that were included in each composite.

Research questions were addressed through 2 x 2 mixed factorial designs which used both between-group and repeated measures to compare mean differences of composites for BD participants who received uridine to those who received placebo pre- and posttreatment. The third research question utilized scatter plots and tested for a quadratic effect of time on mood symptoms for the participants with BD taking uridine.

Between-participant analysis of variance (ANOVA) was used for the first supplemental research question to compare baseline neuropsychological performance of participants with BD to unaffected comparison participants. The second supplemental question summarized and compared academic and educational histories of bipolar and unaffected comparison participants using Fisher's exact test of independence. The third supplemental question used bivariate correlation analyses to examine the relationship between performance on neuropsychological composites and academic experiences.

All analyses were conducted using SPSS. Bonferroni correction was used due to multiple comparisons, statistical significance of $p < .05/6 = .0083$ was used for research questions 1 and 2, and $p < .05/5 = .01$ was used for the first supplemental question.

Table 5. Measures and Scoring by Domain Composite

Domain	Measure	Scores used for composite
Depression	*Children's Depression Rating Scale*	total raw score
	Montgomery-Asberg Depression Rating Scale	total raw score
Attention	*Conners Continuous Performance Test- II*	detectability
		omission errors
		commission errors
		variability
Executive Function	*Wisconsin Card Sorting Test*	perseverative response
		nonperseverative errors
	D-KEFS Trail Making Test	time to complete (in sec)
		total errors
	Color Word Interference Test	inhibition self-corrected errors
		inhibition total time
		inhibition switching sc errors
		inhibition switching time
Working Memory	*Wechsler Intelligence Scale-IV*	digit span total raw score
	Working Memory Index	letter-number sequencing
		total raw score
Verbal Memory	*California Verbal Learning Test-II*	trial 5
		short delayed free recall
		long delay free recall
		recognition
Processing Speed	*Wechsler Intelligence Scale-IV*	coding total raw score
	Processing Speed Index	symbol search raw score

CHAPTER III

RESULTS

Participant Characteristics

There were a total of 30 participants in the study. There were 20 participants in the Bipolar Disorder (BD) group, and their ages ranged from 14 to 21 years old. The mean age of participants in the BD group was 17.6 years old, with a standard deviation of 2.5 years. The ages of participants were similar between the bipolar and comparison groups, with participants in the unaffected comparison (UC) group ranging age from 16 to 21 years and the mean age being 19.0 years with a standard deviation of 1.56. Sixteen participants with BD identified their race as Caucasian, 2 as Native Hawaiian, 1 as Persian, and 1 as multiracial. Two participants with BD identified their ethnicity as Hispanic/Latino. In the unaffected comparison group, 1 participant identified his or her race as multiracial, and 2 participants identified their ethnicity as Hispanic/Latino. There were more female (65%) participants than males (35%) in the BD sample. Table 6 shows the combined means of the bipolar groups on participant characteristics and separate means of the placebo, uridine, and comparison groups, which are similar across most participant characteristics. It is important to note that only 17 participants with BD were included in the final analyses due to 3 being removed for nonadherence. Eighteen participants in the BD group were diagnosed with Bipolar Type 1 and 2 participants

Table 6. Participant Characteristics ($N = 30$).

	Bipolar Participants ($N = 20$)	**Uridine Group ($N = 11$)**	**Placebo Group ($N = 9$)**	**Comparison Group ($N = 10$)**
Mean Age (SD)	17.60 (2.50)	16.91 (2.39)	18.44 (2.51)	19.0 (1.56)
Number of Females (% of sample	13 (65%)	8 (73%)	5 (56%)	5 (50%)
Number of Males (% of sample)	7 (35%)	3 (27%)	4 (44%)	5 (50%)
Psychotropic Meds (% of sample)	14 (70%)	8 (73%)	6 (67%)	0 (0%)
No Medication (% of sample)	6 (30%)	3 (27%)	3 (33%)	0 (0%)
ADHD Diagnosis (% of sample)	6 (30%)	3 (27%)	3 (33%)	0 (0%)
Prior Psych Hospitalization	8 (40%)	4 (36%)	4 (44%)	0 (0%)
Mean WASI-II IQ (SD)	108.59 (13.59)	108.18 (12.89)	108.44 (15.19)	105.8 (8.53)

were diagnosed with Bipolar NOS. Secondary diagnoses included Panic Disorder, Generalized Anxiety Disorder, Social Phobia, Post-Traumatic Stress Disorder, Obsessive Compulsive Disorder, Separation Anxiety Disorder, Specific Phobia, Attention Deficit Hyperactivity Disorder, and Autism Spectrum Disorder. Table 7 lists current and past secondary diagnoses for participants with BD. All participants in the unaffected comparison group did not meet criteria for a DSM-IV diagnosis.

Fourteen participants with BD were taking psychotropic medications during the study and 6 participants were not taking any medications. Participant medications are

Table 7. Secondary Diagnoses for Bipolar Participants

DSM-IV Diagnosis	# Participants	% of sample
Current Secondary Diagnoses		
Panic Disorder	7	35%
Generalized Anxiety Disorder	3	15%
Social Phobia	5	25%
Post Traumatic Stress Disorder	6	30%
Obsessive Compulsive Disorder	6	30%
Separation Anxiety Disorder	3	15%
Specific Phobia	3	15%
ADD/ADHD	6	30%
Autism Spectrum Disorder	3	15%
Past Secondary Diagnoses		
Anorexia Nervosa	1	5%
Bulimia Nervosa	1	5%
Alcohol Abuse	6	30%
Alcohol Dependence	4	20%
Cannabis Abuse	3	15%
Cannabis Dependence	3	15%
Cocaine Abuse	1	5%
Poly Drug Abuse	2	10%
Poly Drug Dependence	1	5%
Obsessive Compulsive Disorder	1	5%

listed in Table 8 and included mood stabilizers (lithium, lamotrigine, divalproex); antidepressants (duloxetine, sertraline, citalopram, bupropion, fluoxetine); antipsychotics (ziprasidone, risperidone, quetiapine); medications for anxiety (hydroxyzine, buspirone, alprazolam, clonazepam); and medications for attention problems (Strattera, Concerta).

Participants were given the WASI-II as an abbreviated measure of IQ. Both groups of participants with BD had similar cognitive scores as the unaffected comparison group. On the two-subtest WASI-II, standard scores of participants with BD ranged from

Table 8. Psychotropic Medications for Bipolar Participants.

Medication	BD Participants	Placebo	Uridine
Mood Stabilizer	9 (45%)	5	4
Lithium	2 (10%)	2	0
Lamotrigine	6 (30%)	3	3
Divalproex	1 (5%)	0	1
Antipsychotic	3 (15%)	2	1
Ziprasidone	1 (5%)	1	0
Risperidone	1 (5%)	1	0
Quetiapine	1 (5%)	0	1
Antidepressant	11 (50%)	4	7
Duloxetine	1 (5%)	0	1
Sertraline	2 (10%)	1	1
Citalopram	2 (10%)	0	2
Bupropion	4 (20%)	2	2
Fluoxetine	2 (10%)	1	1
Anxiety Medication	5 (25%)	2	3
Hydroxyzine	2 (10%)	0	2
Buspirone	1 (5%)	1	0
Alprazolam	1 (5%)	0	1
Clonazepam	1 (5%)	1	0
ADHD Medication	3 (15%)	1	2
Strattera	1 (5%)	1	0
Concerta	2 (10%)	0	2

86 to 136 with a mean of 108.3 and a standard deviation of 13.59. Standard scores of participants in the comparison group on the two-subtest WASI-II ranged from 96 to 118 with a mean of 105.8 and a standard deviation of 8.53.

Results of Research Question 1

Are there significant differences in depressive symptoms after 6 weeks of placebo-controlled uridine administration between adolescents with BD taking uridine (N=11) and those taking a placebo (N=9)?

To address differences between depressive symptoms after 6 weeks of placebo-controlled uridine administration for adolescents with BD taking uridine and those taking the placebo, the depression composite was analyzed using a 2 x 2 mixed factorial design. The pre- and posttreatment measures of the depression composite were used as the repeated-measures factor and the treatment variable (uridine vs. placebo) was used as the between-subjects factor.

Due to Bonferroni correction, all effects are reported significant at $p < .0083$. There was a significant main effect for change in depressive symptoms from pre- to posttreatment, $F(1, 15) = 29.56$, $p < .001$, partial $\eta^2 = .66$. There was no significant main effect for treatment between the uridine and placebo groups, $F(1, 15) < 1$. Furthermore, the results showed that there was not a significant interaction effect between the treatment and depression ratings from pre- to posttreatment, $F(1, 15) = 6.08$, $p > .01$. This indicates that depressive symptoms decreased from baseline to the final visit for participants with BD; however, there was not a significant difference in the report of depressive symptoms between BD participants taking uridine and those taking the

depressive symptoms between BD participants taking uridine and those taking the placebo from pre- to posttreatment. Figure 4 displays the change in the depression composite for the placebo and uridine groups from pre- to posttreatment.

Treatment response in bipolar disorder research has been defined as a reduction of 50% in depressive symptoms on the CDRS-R or MADRS (Patel et al., 2006). Seven of the 17 participants (41% of BD sample) showed a treatment response; however, only 3 of those participants were administered uridine. Table 9 displays the means and standard deviations for the uridine and placebo groups on the CDRS-R and MADRS at baseline and posttreatment.

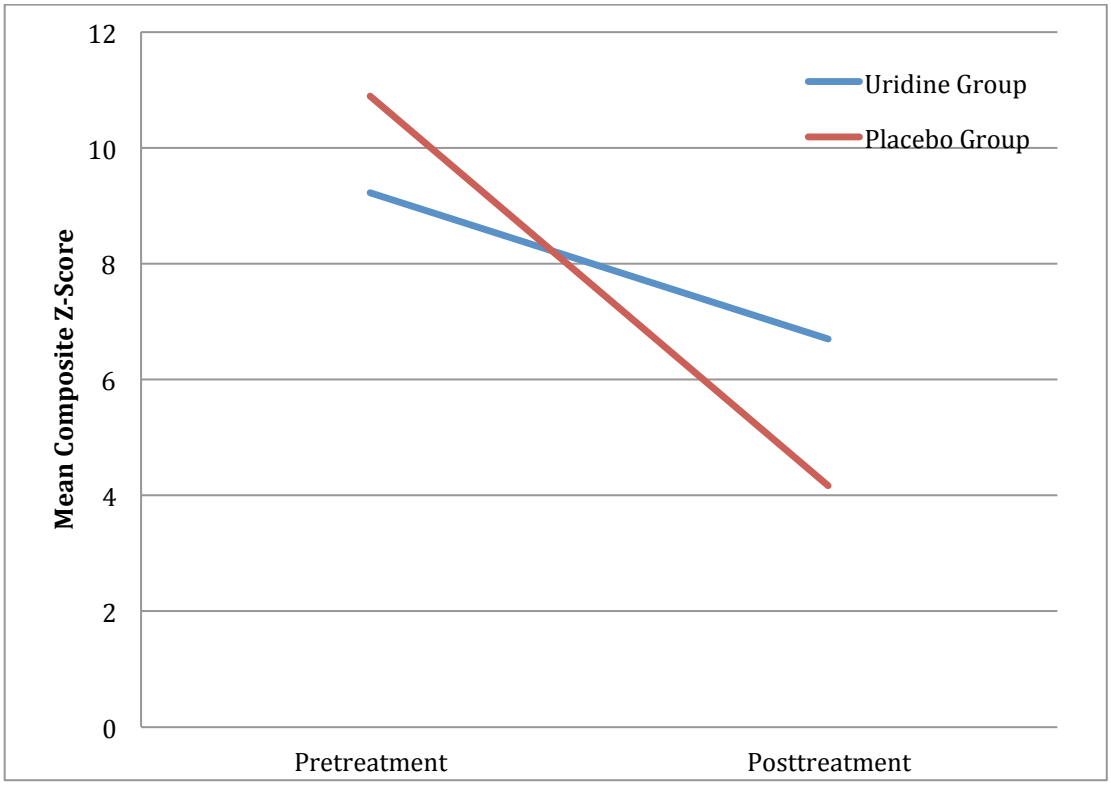

Figure 4. Mean Depression Composite Z-Scores Pre- and Posttreatment.

Table 9. Means and Standard Deviations on Depression Measures

Depression Measure	**Placebo Baseline**	**Uridine Baseline**
CDRS-R	63.75 (5.44)	58.11 (5.23)
MADRS	34.50 (4.75)	28.67 (6.32)
Depression Measure	**Placebo Final**	**Uridine Final**
CDRS-R	37.75 (14.44)	46.89 (14.79)
MADRS	14.25 (10.71)	22.67 (12.04)

CDRS = *Children's Depression Rating Scale-Revised*
MADRS = *Montgomery-Asberg Depression Rating Scale*

Results of Research Question 2

Are there significant differences in performance on neuropsychological tasks (e.g., memory, attention, etc.) after 6 weeks of placebo-controlled uridine administration between adolescents with BD taking uridine (N = 11) and those taking placebo (N=9)?

To address the differences between performance on neuropsychological tasks after 6 weeks of placebo-controlled uridine administration for adolescents with BD taking uridine and those taking the placebo, each neuropsychological composite was analyzed using a 2 x 2 mixed factorial design. The pre- and posttreatment measures for each neuropsychological composite were used as the repeated-measures factors and the treatment variable was used as the between-subjects factor.

Attention

The CPT-II was administered to both groups to assess attention pretreatment and following 6 weeks of placebo-controlled uridine administration. A 2 x 2 mixed factorial design was used to compare mean attention composite scores to determine if there were

any differences between the uridine and placebo groups from pre- to posttreatment. Results revealed that there was a significant main effect for change in attention from pre- to posttreatment, $F(1, 15) = 12.74$, $p < .01$, partial $\eta^2 = .46$. There was no significant main effect for treatment between the uridine and placebo groups, $F(1, 15) = 1.64$, $p > .05$. The results showed that there was no significant interaction effect between the treatment and attention performance from pre- to posttreatment, $F(1, 15) < 1$. Both the uridine and placebo groups improved in performance in attention on the CPT-II from baseline to posttreatment; however, there were no significant differences between the groups. Figure 5 displays the changes in the attention composite for the placebo and uridine groups from pre- to posttreatment. Additionally, Table 10 displays the z-scores of neuropsychological composites based on performance by participants in the uridine and placebo groups at the baseline and following 6 weeks in the study.

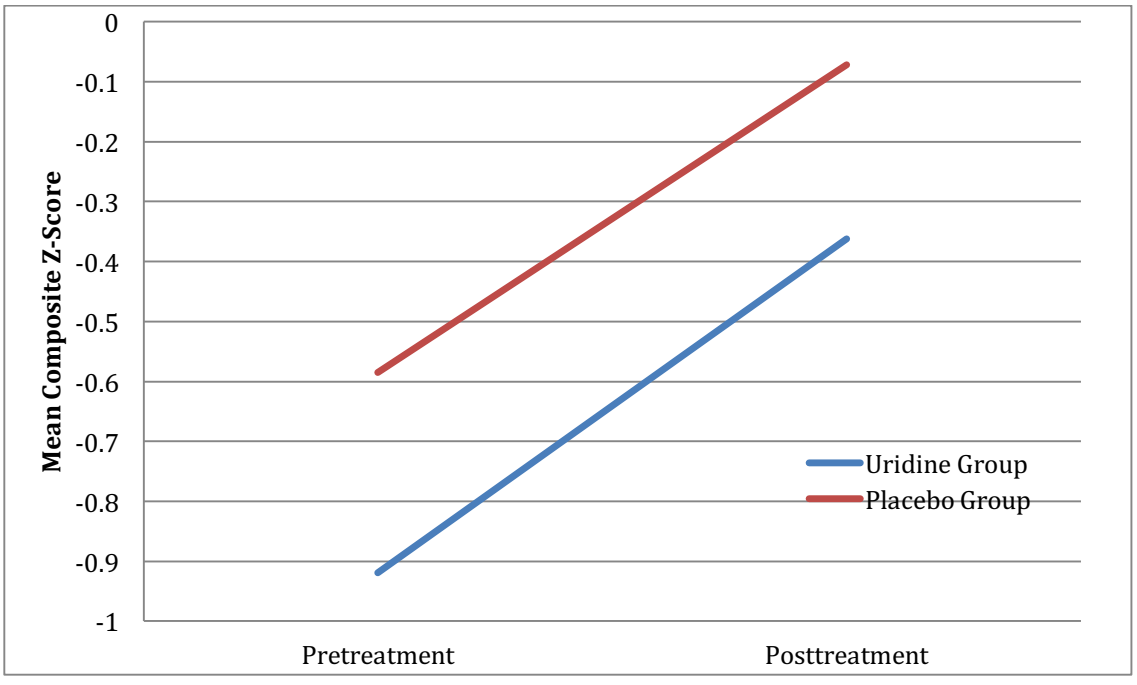

Figure 5. Mean Attention Composite Z-Scores Pre- and Posttreatment

Table 10. Z-Scores and Standard Deviations on Neuropsychological Domains for Participants With BD

Neuropsychological Domain	Placebo Baseline	Uridine Baseline	Placebo Final	Uridine Final
Attention	-.5851 (1.25)	-.9192 (0.82)	-.0722 (0.98)	-.3618 (0.85)
Executive Function	-.4543 (0.77)	-.4682 (0.86)	.0855 (0.68)	.4000 (0.69)
Working Memory	-.2665 (1.26)	-.3878 (1.13)	-.2325 (0.89)	-.3369 (1.18)
Verbal Memory	-.6610 (0.79)	-.3785 (1.39)	-.3968 (1.27)	-.0318 (1.49)
Processing Speed	-.2590 (1.54)	-.4549 (1.56)	-.2446 (1.49)	-.1617 (1.51)

Executive Functioning

Performance in executive functioning was examined using subscales from the TMT, CWIT, and the WCST. These measures were administered to BD participants at baseline and posttreatment treatment to examine executive functioning performance. Table 10 displays z-scores of the executive functioning composite for both treatment groups at baseline and the final visit. A 2 x 2 mixed factorial design was used to compare mean executive functioning composite scores to determine if there were any differences between the uridine and placebo groups from pre- to posttreatment.

Results revealed that the main effect for change in performance on executive functioning from pre- to posttreatment was significant, $F(1, 15) = 16.19$, $p < .01$, partial $\eta^2 = .52$. This indicates that participants with BD improved their performance on executive functioning tasks from pre- to posttreatment. There was no significant main effect for treatment between uridine and placebo groups, $F(1, 15) < 1$. The interaction between treatment and executive functioning performance from pre- to posttreatment was also not significant. This suggests that overall the bipolar group improved performance in executive functioning from baseline to posttreatment, but there was not a significant difference in executive functioning performance between the uridine and the placebo groups from pre- to posttreatment. Figure 6 displays the executive functioning composite for the placebo and uridine groups from pre- to posttreatment.

Working Memory

Participants were administered the Working Memory composite of the WAIS-IV to assess working memory. A mixed 2 x 2 factorial design was used to compare mean

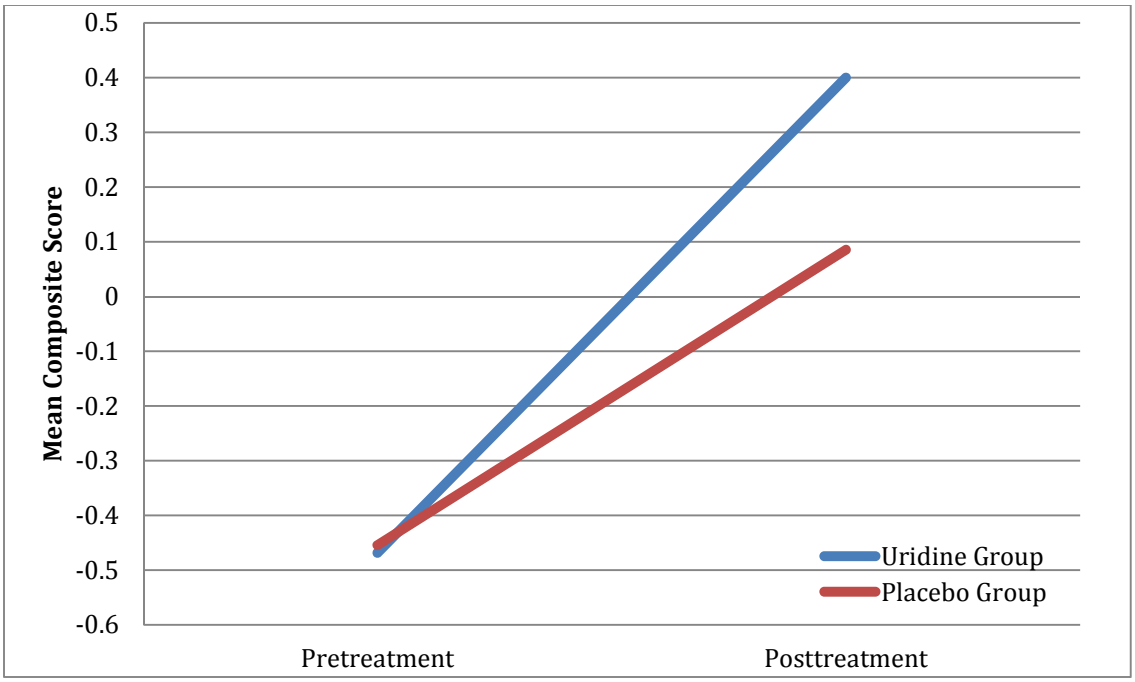

Figure 6. Mean Executive Functioning Composite Z-Scores Pre- and Posttreatment

working memory composite scores to determine if there were any differences between the uridine and placebo groups from pre- to posttreatment. Results revealed that there was not a significant main effect for change in working memory, $F(1, 15) < 1$. Working memory performance proved to be consistent for participants with BD. There was not a significant main effect for treatment between uridine and placebo groups, $F(1, 15) < 1$. Also, there was not a significant interaction effect between the treatment and working memory performance from pre- to posttreatment, $F(1, 15) < 1$. The working memory composite for the placebo and uridine groups from pre- to posttreatment is illustrated in Figure 7. Memory scores for participants in the placebo and uridine groups were similar and there was not a significant difference in performance between the groups from baseline to final visit.

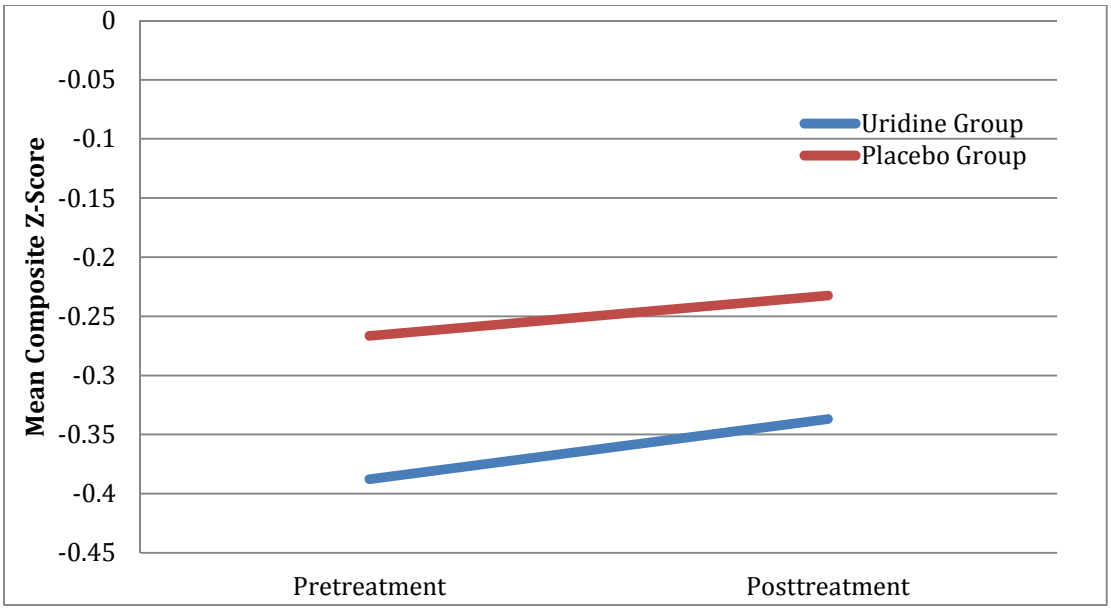

Figure 7. Mean Working Memory Composite Z-Scores Pre- and Posttreatment

Verbal Memory

Participants with BD were administered the CVLT-II pre- and posttreatment to assess verbal memory. A mixed 2 x 2 factorial design was used to compare mean verbal memory composite scores to determine if there were any differences between the uridine and placebo groups from pre- to posttreatment. The main effect of change in verbal memory from pre- to posttreatment was not significant, $F(1, 15) < 1$. Participants with BD scored similarly on the CVLT-II over time. There was no significant main effect for treatment between uridine and placebo groups, $F(1, 15) = 2.37$, $p > .05$. Further, the results failed to show a significant interaction between the BD treatment groups and verbal memory performance from pre- to posttreatment, $F(1, 15) = 1.13$, $p > .05$. As displayed in Figure 8, both participants taking uridine and participants taking placebo showed little change in performance on verbal memory, and there was not a significant difference in performance between the two groups with treatment.

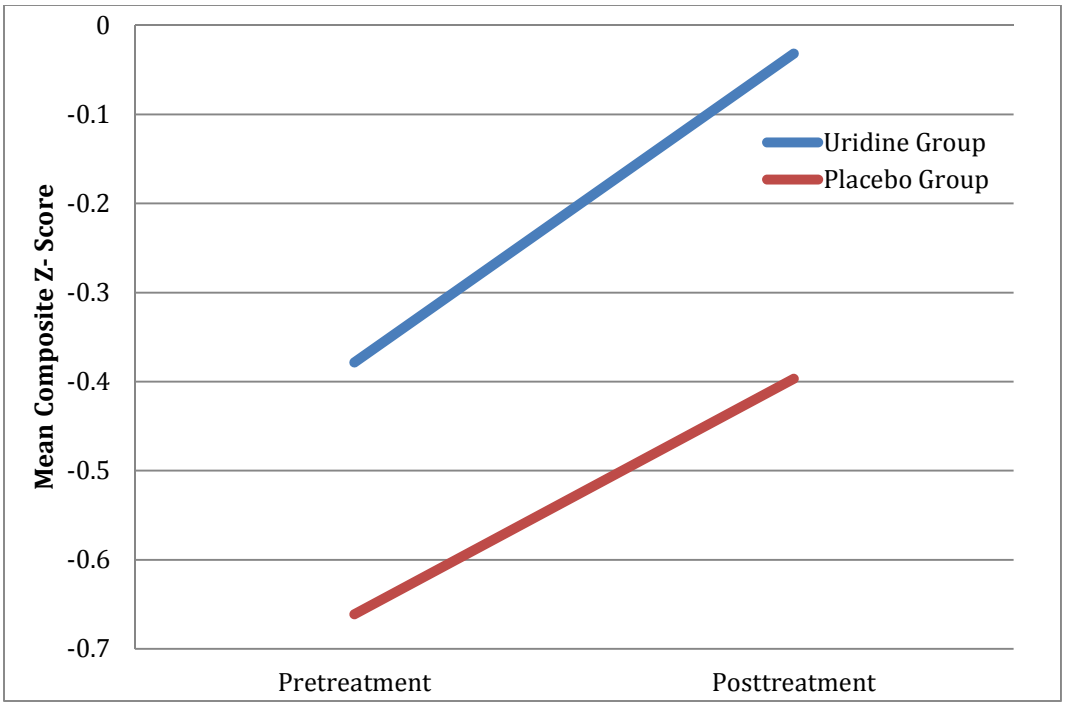

Figure 8. Mean Verbal Memory Composite Z-Scores Pre- and Posttreatment

Processing Speed

Measures from the WAIS-IV, including the Coding and Symbol Search subtests, were administered to participants with BD pre- and treatment to assess processing speed. Table 10 displays z-scores for the processing speed composite for both groups at baseline and after 6 weeks of treatment. A mixed 2 x 2 factorial design was used to compare mean processing speed composite scores to determine if there were any differences between the uridine and placebo groups over time. Figure 9 displays the executive functioning composite for the placebo and uridine groups from pre- to posttreatment.

There was no significant main effect for change in processing speed from pre- to posttreatment, $F(1, 15) = 8.49$, $p > .05$. Participants with BD performed similarly on processing speed measures at baseline and posttreatment. There was not a significant

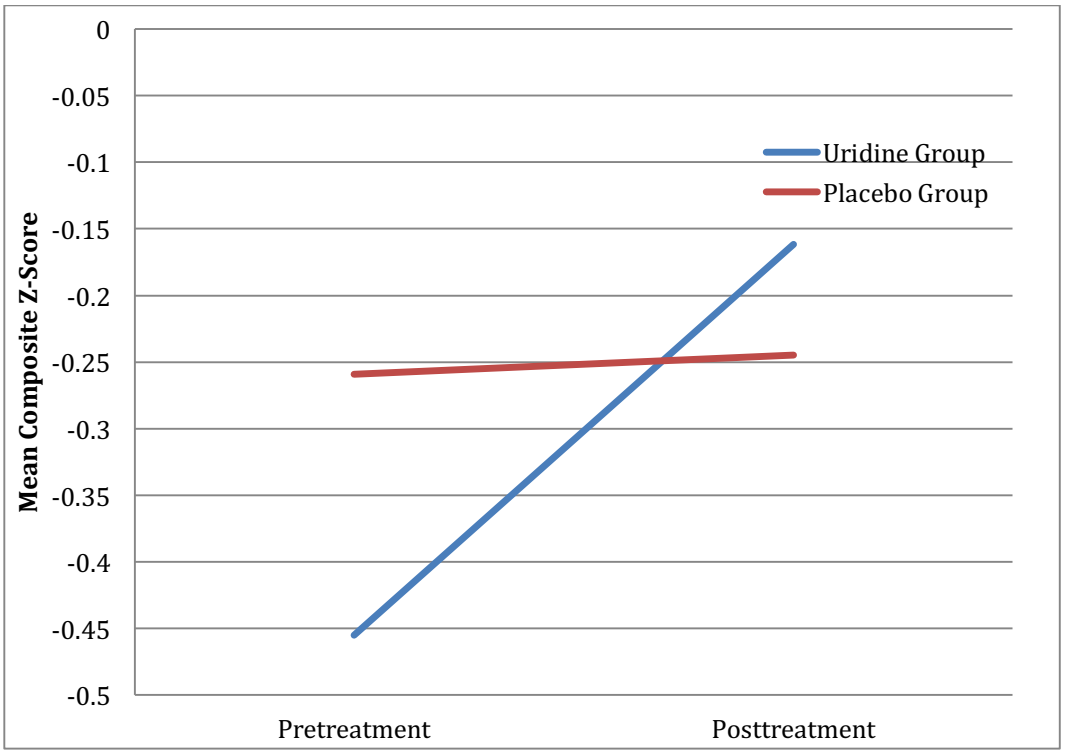

Figure 9 Mean Processing Speed Composite Z-Scores Pre- and Posttreatment

main effect for treatment between uridine and placebo groups, $F(1, 15) = 1.64$, $p > .05$. Additionally, the results showed that there was not a significant interaction effect between the treatment and processing speed performance from pre- to posttreatment, $F(1, 15) < 1$. This indicates that there was not a significant difference in processing speed performance between BD participants taking uridine and those taking the placebo from pre- to posttreatment.

Results of Research Question 3

For adolescents with BD taking uridine, is there a quadratic effect of time on depressive symptoms?

To test for a quadratic effect of time of uridine on depressive symptoms,

depressive ratings were analyzed for BD participants taking uridine. Scatter plots were utilized to visually analyze depression ratings for participants throughout the study.

Depression ratings from each week of the larger placebo-controlled uridine study were plotted to evaluate the change in depression scores. Figure 10 displays the uridine and placebo groups mean CDRS-R depression ratings change over the course of the larger study. This graph revealed that the biggest change in mean depression scores for the uridine and placebo groups occurred during the 1st week of the study. There was approximately a 10-point decrease in mean CDRS-R scores from the baseline visit to the week 1 visit for both the uridine and placebo groups. Following the 1st week study, the uridine group leveled off and the placebo group continued to slowly improve.

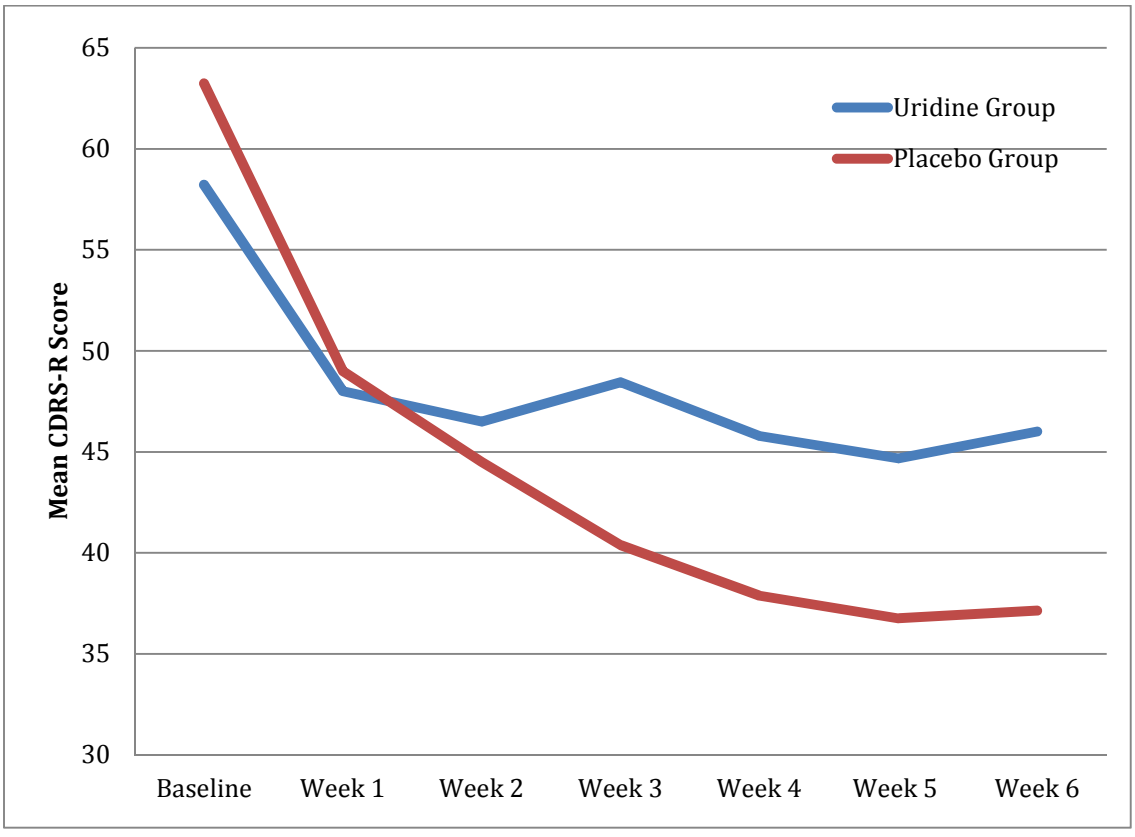

Figure 10. Mean CDRS-R Scores for Uridine and Placebo Groups Across Study One

Further analysis of all CDRS-R scores and MADRS scores for participants in the uridine group throughout the placebo-controlled uridine study utilizing scatter plots revealed that 3 participants had a greater decrease in depression ratings than the rest of the group. In fact, these were the 3 participants that had a treatment response to uridine. For the 3 participants that had a treatment response, the greatest decrease in scores happened during the 1st week that participants were taking uridine. Following that week, there was a small steady decrease in depression scores that ranged 5 to 10 points. For the other participants in the uridine group, there was minimal change over time in depression scores. Furthermore, there did not appear to be a quadratic effect of time of uridine on depressive symptoms for participants in the uridine group.

Results of Supplemental Research Question 1

What are the differences in prestudy performance on neuropsychological tasks between comparison subjects (NB=10) and depressed adolescents with BD (N=20)?

To address the differences between performance on neuropsychological tasks between nonaffected comparison subjects and adolescents with BD, each neuropsychological composite was analyzed using between-subjects analysis of variance (ANOVA). The baseline treatment measures for each neuropsychological composite were used as dependent variables and the group (bipolar disorder vs. unaffected) was the between-subjects factor. Due to multiple neuropsychological comparisons, Bonferroni correction was used and all effects are reported with a statistical significance level of $p < .05/5 = .01$.

Attention

Between-subjects ANOVA compared mean attention composite scores from baseline for participants with BD and unaffected comparison participants to determine if there were any differences between groups. Results of the ANOVA demonstrated that attention performance differed between the two groups, $F(1, 28) = 6.58$, $p < .05$. However, these differences were not considered to be statistically significant ($p = .016$). On the CPT-3, participants with BD made more errors of commission and omission than unaffected comparison participants. Additionally, participants with BD had more difficulty distinguishing the target from nontargets (detectability) and were more variable (less consistent) when responding; however, these differences were not statistically significant. Figure 11 illustrates the mean difference between groups. Table 11 displays the means and standard deviations of measures that contribute to neurocognitive composites based on performance by participants in the BD and comparison groups.

Executive Functioning

Between-groups ANOVA was used to determine if the participants with BD and comparison participants differed on executive performance. Results showed that executive functioning performance differed significantly between the two groups, $F(1, 28) = 4.23$, $p < .05$, but not at the $p < 01$. Figure 11 displays that participants with BD performed worse than comparison participants on tasks that involved response inhibition and set shifting, but there was not a statistically significant difference between groups.

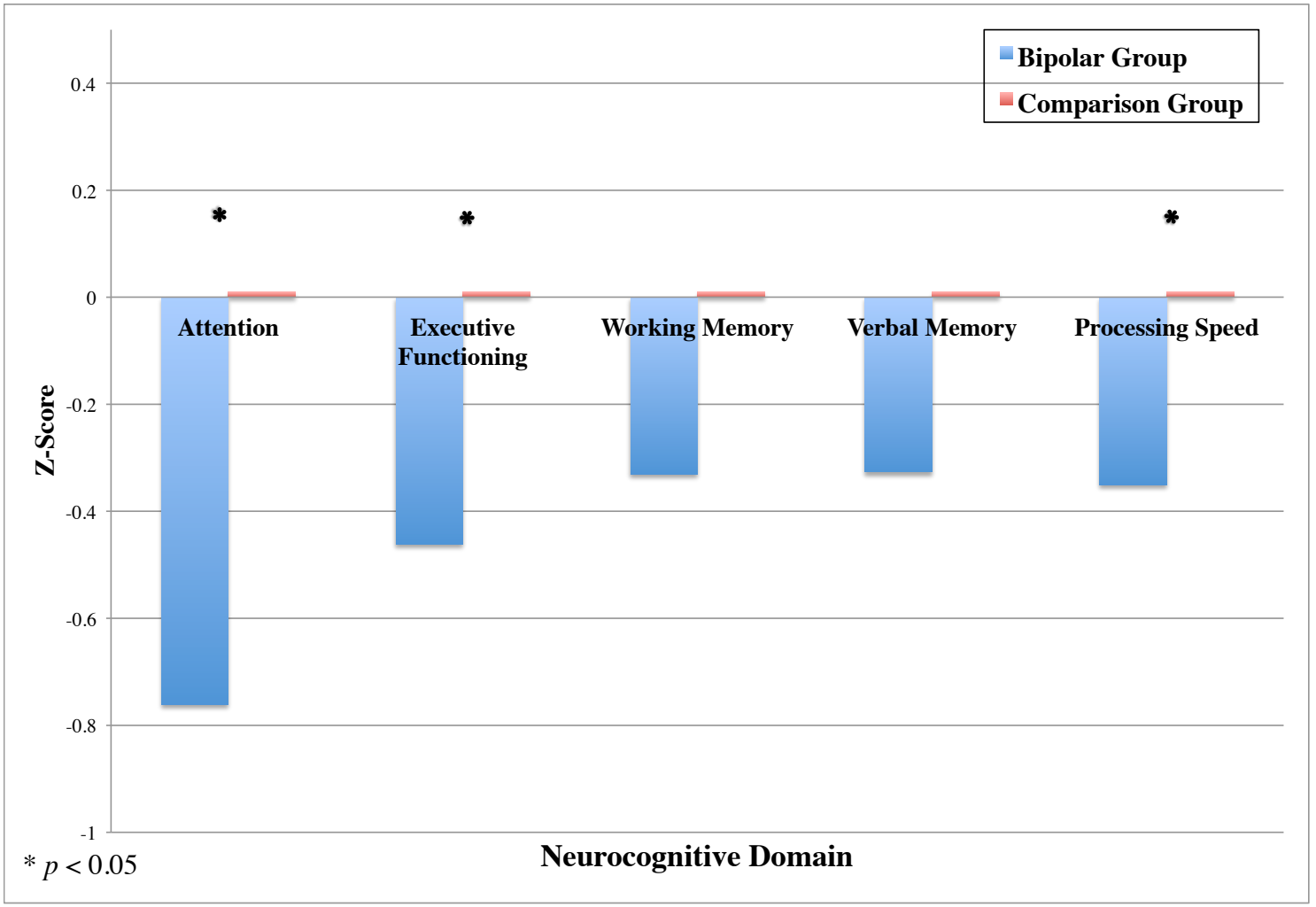

Figure 11. Mean Z-Scores of Each Neurocognitive Domain for Bipolar and Comparison Participants at Baseline Administration.

Table 11. Z-scores and Standard Deviations on Neuropsychological Domains for All Participants

Neuropsychological Domain	Bipolar Group Baseline	Comparison Group Baseline	Bipolar Group Final	Comparison Group Final
Attention	-.7620 (1.03)	.0000 (0.88)	-.2255 (0.90)	-.1661 (1.27)
Executive Function	-.4617 (0.80)	.0000 (0.67)	.2520 (0.69)	-.0861 (0.81)
Working Memory	-.3308 (1.16)	.0000 (0.94)	-.2878 (1.02)	.0947 (1.18)
Verbal Memory	-.3271 (1.30)	.0000 (0.81)	-.3111 (1.40)	.0567 (1.49)
Processing Speed	-.3508 (1.50)	.0000 (0.94)	-.2007 (1.45)	.3995 (1.21)

Working Memory

Between-subjects ANOVA that compared mean working memory between participants with BD and unaffected comparison participants did not demonstrate a main effect between groups, $F(1, 28) = 1.87$, $p > .05$. This means that there were no significant differences in performance on working memory tasks at baseline between participants with bipolar disorder and unaffected comparison participants.

Verbal Memory

Similarly, between-subjects ANOVA that compared mean verbal memory at baseline between participants with BD and unaffected comparison participants did not demonstrate a main effect between groups, $F(1, 28) = 2.92$, $p > .05$. This suggests that performance on verbal memory items from the CVLT-II was similar between participants with bipolar disorder and unaffected comparison participants.

Processing Speed

Between-subjects ANOVA compared mean processing speed composite scores from baseline for participants with BD and unaffected comparison participants to determine if there were any differences between groups. Results of the ANOVA revealed that processing speed performance differed between the two groups, $F(1, 28) = 3.48$, $p < .05$, but was not statistically significant. Figure 11 demonstrates that comparison participants outperformed participants with bipolar disorder on processing speed tasks. Although not quite statistically significant, these findings are important. These outcomes are not unexpected and longitudinal studies have shown that processing speed deficits are associated with functional outcomes for individuals with BD (Burdick et al., 2010).

Results of Supplemental Research Question 2

What are the differences in prior educational experiences between unaffected comparison participants and adolescents with BD?

Fisher's exact test of independence was used to examine the differences in educational experiences between participants with BD and unaffected comparison participants. Each categorical educational variable (see Appendix B for Academic and Educational History Report Form) was analyzed between the bipolar and comparison group using Fisher's exact test. As shown in Table 12, the mean number of years of education for unaffected comparison participants was 12 years with a standard deviation of 1.49 years, while participants with BD had a mean of 11.05 years of education and a standard deviation of 2.33 years. Despite a similar number of years of education, the educational experience reported by many of the bipolar participants was relatively different than unaffected comparison participants. Analyses of participant self-reports using Fisher's exact test indicted that participants with BD were more likely to report academic difficulties than unaffected comparison participants (p =.002).

According to participant report regarding educational experiences, many participants with BD reported absences from school and the inability to complete assignments/homework during extreme mood episodes. Bipolar participants reported that during a mood episode they had fallen behind in coursework, which resulted in feeling overwhelmed and unable to make up work before the grading term was over. Applying Fisher's exact test, participants with BD were more likely to report discontinuing education (p = .029) than unaffected comparison participants. Eight of the participants with bipolar disorder (40%) reported discontinuing a program, school, or college due to difficulties associated with a mood episode, primarily depression. Six

Table 12. Participant Educational Characteristics.

	BD Participants ***N*** **= 20**	**Comparison Participants** ***N*** **= 10**
Years of Education (SD)	11.05 (2.33)	12.00 (1.49)
Academic Difficulties	12 (60%)	0 (0%)
Discontinued Education	8 (40%)	0 (0%)
Break from School	6 (30%)	1 (10%)
Transferred Programs/Schools	9 (45%)	0 (0%)
Alternative School/Program	5 (20%)	0 (0%)
Had IEP or 504 Plan	5 (25%)	0 (0%)

participants with BD stated that they experienced a severe mood episode that resulted in a break from school, which was associated with hospitalization for 4 participants. One unaffected comparison participant was taking a semester break from college due to financial reasons. No statistically significant differences were observed with Fisher's exact test between bipolar or comparison participants with regard to taking a break from school (p = .37).

According to Fisher's exact test, participants with BD were more likely to transfer to new programs or schools than comparison participants (p = .013). Nine participants transferred to different schools, programs, or colleges when they experienced difficulty during a bipolar episode. Five participants reported attending alternative schools or programs; 2 of the students elected to complete courses exclusively online. The 2 participants who completed online courses reported that this was a flexible alternative to

live courses and that courses online helped them manage anxiety. Additionally, two participants transferred out of International Baccalaureate (IB) and honors courses to mainstream courses so that the workload was more manageable. Using Fisher's exact test, no statistically significant differences were observed between bipolar or comparison participants in attending alternative programs/schools ($p = .14$).

Four participants with bipolar disorder stated that they had an Individualized Education Program (IEP) and received special education services at school. Of these, 3 participants had IEPs for emotional and behavioral disorders and 1 participant had an IEP for math. One participant reported that she had a 504 plan and received accommodations at school for her diagnoses of BD and ADD. However, no statistically significant differences were found between bipolar or comparison participants in the study receiving special education services using Fisher's exact test ($p = .14$).

Results of Supplemental Research Question 3

Is there a relationship between performance on neuropsychological tasks and academic difficulties for participants with BD?

To investigate the relationship between performance on neuropsychological tasks and reports of academic difficulties, each baseline neuropsychological composite was correlated with participants' report of having academic difficulties. This was done using bivariate correlations. As seen in Table 13, there was a significant relationship between participants who received special education services and their performance on tests of attention, $r = -.375$, $p < .05$, working memory, $r = -.539$, $p < .01$, executive functioning, $r = -.611$, $p < .001$, and processing speed, $r = -.572$, $p < .01$. Receiving special education

Table 13

Correlation Matrix for Academic Difficulties and Composites

	Depression	Attention	Working Memory	Executive Function	Verbal Memory	Processing Speed
Special Education	-.376	-.375*	-.539**	-.611**	-.330	-.572**
Academic Difficulties	.085	-.394*	-.381*	-.315	-.054	-.459*
Alternative Education	-.054	-.228	-.307	-.274	.112	-.442*
Discontinued Education	.179	-.198	-.001	-.160	.122	-.303
Transferred Education	.139	-.199	-.112	-.151	.005	-.365*
Break from Education	.392	-.000	-.040	.062	.086	.017
ADHD Diagnosis	-.281	-.135	-.367*	-.225	-.231	-.184
Psychiatric Hospitalization	.186	-.181	-.074	-.071	.042	-.154
WASI-II Score	.206	.394*	.485**	.604**	.203	.516**

**$p < .01$, *$p < .05$

services was associated with lower performance on attention, working memory, executive function, and processing speed tasks. Additionally, there was a significant relationship between reported academic difficulties and attention, $r = -.394$, $p < .05$, working memory, $r = -.381$, $p < .05$, and processing speed, $r = -.375$, $p < .05$. Participants who self-reported experiencing academic difficulties had more attention, working memory, and processing speed deficits.

There was a significant relationship between participants enrolled in alternative education programs or schools and processing speed task performance, $r = -.442$, $p < .05$. Enrollment in alternative classes, programs, or schools was associated with lower processing speed scores. Additionally, participants who had transferred to new classes, programs, or schools had a significant relationship with processing speed test performance, $r = -.365$, $p < .05$. Lower processing speed performance was associated with transferring to different classes, programs, and schools. A significant correlation was found for participants with an ADHD diagnosis in terms of working memory test score ($p < .05$); surprisingly, it was not significantly correlated with lower scores on attention or processing speed.

Furthermore, the total score on the WASI-II, an abbreviated test of intelligence comprised of Vocabulary and Matrix Reasoning, was significantly correlated with attention ($p < .05$), working memory ($p < .01$), executive functioning ($p < .01$), and processing speed ($p < .01$). Higher scores on the WASI-II were correlated with higher performance on tasks of attention, working memory, executive functioning, and processing speed.

CHAPTER IV

DISCUSSION

Currently, there are no treatments designed specifically for use with adolescent bipolar depression. Many psychotropic medications that are used to treat bipolar depression may further exacerbate pre-existing neurocognitive deficits experienced by these youth. This study was an attempt to study the efficacy of uridine as a novel treatment for depression. Uridine is among similar pyrimidines that have shown success in reducing depressive symptoms in previous studies of BD adults and adolescents. Pyrimidines, including uridine, have shown neurocognitive benefits such as increased attention and working memory performance in healthy participants. Thus, this study set out to evaluate the effects of uridine on depressive symptoms and the potential enhancement of cognitive functioning.

Furthermore, the current study intended to replicate previous findings of neuropsychological deficits in youth with bipolar disorder in a depressed episode. This study also examined the association between neuropsychological performance and educational experience for youth with BD.

Major Research Findings

Treating Bipolar Depression With Uridine

In the efficacy analysis, both groups of BD participants showed significant improvements in the depressive symptoms from baseline to week 6, although participants treated with uridine did not differ significantly from those administered a placebo with regard to decreasing symptoms of depression. Thirty-three percent of participants with BD who were administered uridine showed a treatment response. This can be compared to treatment response rates of 50 to 56% in randomized, double-blind, placebo-controlled trials of pharmacotherapies used as treatment for bipolar depression (Iovieno, Walker, & Papakostas, 2014). Cytidine and TAU have shown response rates of 53 to 55% in decreasing depressive symptoms in adults with bipolar disorder in previous clinical trials. However, in a placebo-controlled trial of cytidine as an adjunctive therapy to valproate, there was not a significant difference between cytidine and placebo response rates (53% vs. 47%) after 12 weeks of treatment (Yoon et al., 2009).

The placebo response in the present study was 50%, which is high but not uncommon. Placebo response in treatment trials for participants with bipolar disorder has proven to be a challenge, with the placebo response rate as high as 40 to 55% in randomized, double-blind, placebo-controlled trials for bipolar depression (Iovieno et al., 2014). Furthermore, it is important to consider that up to 52% of antidepressant trials of bipolar depression and 40% of trials on bipolar mania fail to distinguish the active treatment from the placebo (Vieta & Carne, 2005).

It should be noted that 11 out of 20 participants with BD in the study were taking antidepressants, and 7 of these participants were in the uridine group. Taking

antidepressants alone as a treatment for bipolar depression is contraindicated, as antidepressants have been reported to increase irritability and switching to mania (McInemey & Kennedy, 2014). No participants with BD in the study switched to mania as evidenced by YMRS scores > 12; however, the use of antidepressant medications could have affected participant outcomes. Antidepressants increase the amount of serotonin in the brain and uridine is purported to increase brain dopamine. The interaction between brain dopamine and serotonin due to taking both uridine and antidepressants in individuals with bipolar disorder is unknown. More research is needed to evaluate the efficacy of uridine as a treatment for youth with bipolar depression.

Neurocognitive Deficits in Bipolar Disorder

Attention was measured with the *Conners Continuous Performance Test-Third Edition, (CPT-3)*. Participants with BD made more omission and commission errors, and were less able to detect the target from nontargets when compared to performance of the unaffected comparison group on the CPT-3. Additionally, participants with BD performed worse on executive functioning measures, including the Wisconsin Card Sorting Task, the Color Word Interference Test, and the Trail Making Number-Letter Switching Test, than the unaffected comparison group. Furthermore, participants with BD performed slower on processing speed tasks, the Coding and Symbol Search subtests from the WAIS-IV, when compared to the unaffected comparison group.

In summary, participants with BD revealed performance deficits in attention, executive functioning, and processing speed. Due to correction for multiple comparisons, no statistically significant differences were observed between bipolar youth and

unaffected comparisons. The current study did not have the power to show the robust effect of neuropsychological deficits for participants with bipolar disorder compared to unaffected comparison participants; however, differences were observed.

Deficits in these areas could be better explained by medications that the participants were taking (Henin et al., 2007). Additionally, all participants with BD were in a current state of depression, which could have further impaired neuropsychological functioning; however, there is evidence that neurocognitive deficits persist regardless of the mood state. An increase in attention and executive functioning performance with improvement of depressive symptoms could suggest that participants may be less impaired in these domains during euthymia or as symptoms of depression decrease.

Effects of Uridine on Neurocognitive Performance

Both the uridine and placebo groups increased their attention and executive functioning performance from baseline to week 6. Results found no difference between the uridine and placebo groups in performance on any of the neuropsychological composites from pre- to posttreatment. While results from this study did not provide evidence for uridine as a neurocognitive enhancer, it did not appear to have a negative effect on cognition. This is an important consideration, as many of the available treatments for adolescent bipolar depression can have a considerable negative impact on cognition.

Improved attentional performance has also been found with citicoline, a pyrimidine that breaks down into uridine and choline, in a study of healthy adult women and adolescent males (McGlade et al., 2015; McGlade et al., 2012).

Both of these studies found that with daily oral administration of citicoline, performance on the CPT-II improved; adult women made fewer omission and commission errors and adolescent males had improved detectability and lower commission errors.

Due to weight variation among participants in the citicoline study with adolescent males, dose by weight was calculated and used in the analyses (McGlade et al., 2015). In the current study, participants ranged in weight from 90 to 358 lbs. Furthermore, the participants that weighed the most and the least only differed by 1 year in age and grade level, yet had a difference in weight of 268 lbs. Therefore, participant weight and metabolism may have affected the dose and effectiveness of uridine for participants.

Results of the CPT-3 suggested that the mean performance of both groups of participants with BD improved during the study. Since participants with BD also had a mean overall decrease in depression, one possible explanation for these results is that a decrease in depressive symptoms resulted in improved attention performance. An alternative explanation for the improvement in attention performance may be due to practice effects. Participants may improve performance after exposure to the CPT-3 by decreasing omission and commission errors, and increasing detectability and variability due to prior testing. The same explanations can also be applied to the improvement in executive functioning performance of participants with BD.

While uridine may not have had a negative effect on cognition, it may have attenuated practice-induced learning with repeated exposure. Research has shown practice effects in healthy volunteers for the WCST across 12 months (Basso et al., 2001) and on the TMT across 3 weeks (Buck, Atkinson, & Ryan, 2008). The CPT-3 was assessed for test-rest reliability and practice effects at a 1-to 5-week interval. Results for

120 participants revealed that omission errors, perseveration errors and variability stayed consistent over time; however, detectability (cohen's *d* = -.21) and commission errors (Cohen's *d* = -.31) decreased at the second administration (Conners, 2014).

Results from the comparison group showed that neurocognitive performance from the baseline to 6 weeks later was relatively stable, except for the processing speed task. Participants in the comparison group showed significant improvement in processing speed performance following 6 weeks. Practice effects on WAIS-IV have been shown to occur in the Processing Speed Composite across 3- and 6-month intervals. A sample of 54 participants with average intelligence improved approximately 9 points on the Processing Speed Composite at either interval (Estevis, Basso, & Combs, 2012). In contrast, participants with BD did not have the same improvement in processing speed, but showed improvement in other domains.

Academic Experiences and Challenges With Bipolar Disorder

Youth with BD reported many difficulties and challenges academically. The majority of participants with BD had an interruption or discontinuation in education. Additionally, some participants received special education services or attended alternative classes, programs, or schools. Almost half of the participants with BD found that transferring to a new program, school, or college was helpful.

Even though participants with BD experienced challenges and academic difficulties, most of the participants with BD were high-achieving students and had educational goals that they strived to accomplish, much like the unaffected comparison participants. Only 2 of the participants with BD had discontinued school and had been

unable to return, but still had intentions of attending in the future.

Most of the participants with BD did not report experiencing persistent academic difficulties (e.g., in reading or math). In fact, only a quarter of the participants qualified for special education services and many of them received services for emotional and behavioral difficulties. Additionally, 2 of the students that were attending alternative classes or schools were doing so for social/emotional reasons. Many of the participants reported that symptoms of depression and mania had a huge impact on their academic and/or occupational functioning (e.g., difficulty concentrating, lassitude, fatigue, psychomotor retardation, distractibility, racing thoughts, irritability, pressured speech, restlessness). Furthermore, once a mood episode worsened, many participants reported they often were not able to continue attending school or keep up with assignments and homework. Participants with BD reported the most academic difficulties during a severe depressive episode.

Association Between Neurocognitive Deficits and Academic Experiences in BD

There was an association between academic difficulties and neurocognitive performance for participants with BD on attention, working memory, executive functioning, and processing speed. Participants with BD who received special education services had lower attention, working memory, executive functioning, and processing speed performance.

Since neurocognitive deficits have been known to persist despite mood episodes, these deficits may affect how students are able to plan, learn, socialize, and function academically. Students with BD who have neuropsychological deficits that impair

academic performance may require an individualized education program and specialized instruction in order to be successful at school.

It is important to consider that much of the cognitive testing that goes into qualification for special education services includes measurement in the areas of attention, working memory, executive functioning, and processing speed as part of the assessment process. Therefore, if students perform poorly in those areas, it may impact whether or not they qualify for special education services; however, most of the participants with BD who reported receiving special education services noted that they did so for emotional and behavioral difficulties. Participants were most likely referred or identified, and qualified for specialized education services based on emotional and behavioral needs, and academic testing may not have been the focus of eligibility. In fact, only 1 participant with BD reported having an IEP for math.

BD participants who had more attention, working memory, and processing speed deficits self-reported experiencing academic difficulties specific to classes and mood episodes, and also centered on symptoms involved in mood episodes. Participants reported difficulty with a certain course, specific teacher, lots of homework, or a project assigned. Additionally, participants stated that once a mood episode began, they were unable to continue attending school, keep up with assignments, or complete homework. Participants did not report academic difficulty with reading, writing, or math that persisted over time. Many participants stated that they had difficulty with certain symptoms of BD that impacted academic performance. For participants who experienced extreme mood symptoms/episodes that had an impact on school attendance and learning, it was apparent that 504 accommodations could benefit them during these episodes.

This study did not find the same rates of reading, writing, and math difficulties that have previously been reported in youth with BD, especially those with neuropsychological deficits (Pavuluri, O'Connor, et al., 2006). The majority of the participants reported that their academic difficulties were not persistent; rather they occasionally failed a course, dropped out of a program, transferred to a new school, or had to retake an entire semester. This may be due to the fact that a higher functioning group of participants with BD with higher cognitive ability were enrolled in the study.

There was an association of lower processing speed performance with enrollment in alternative classes or schools for participants with BD. Additionally, lower processing speed performance was associated with transferring to different classes, programs, and schools. It is not surprising that participants with BD who have processing speed deficits have transferred to alternative programs or new schools to complete their classes. In a 15-year follow-up study, processing speed deficits in participants with BD were strongly associated with decreased social and global functioning (Burdick et al., 2010). Almost half of the participants with BD reported transferring to a new environment due to social or academic difficulties. These participants may feel more comfortable in alternative educational settings or transfer to programs or universities that are a better fit for them.

Bipolar participants who had an ADHD diagnosis had lower working memory scores. Working memory tasks required the recall of digits forward, backward, and arranging digits in mental order and then mentally ordering sequences of letters and numbers. Participants with ADHD had significant deficits recalling numbers backwards. Thirty percent of the bipolar participants were diagnosed with ADHD and half of those participants were already taking medication for ADHD. Since participants with ADHD

did not have deficits in any domains other than memory, one explanation for these results is that medications for ADHD may have improved performance on attention and other neurocognitive tasks.

As performance on the WASI-II increased, so did performance on attention, working memory, executive functioning, and processing speed tasks. Participants with the highest WASI-II scores did not experience deficits in baseline neuropsychological performance compared to unaffected controls. Bipolar participants who performed higher cognitively and neuropsychologically than other participants also appeared to have a high range of functioning. Many of these participants were attending college and working, and had social relationships. Surprisingly, participants with the highest WASI-II scores also had the most severe depression scores and the most extreme histories of hospitalizations. It appeared when these participants experienced extreme mood episodes, they reported interruption and significant impairment in many if not all areas of functioning (e.g., social, academic, and occupational). Additionally, these participants had serious histories of suicidal ideation and past suicide attempts.

Safety and Tolerability

There were no serious adverse events that took place during the study and participants did not report a significant number of adverse events. As shown in Table 14, participants in the uridine group reported more adverse events than those in the placebo group, but 35.7% of those events were related to the treatment. There were several other adverse events reported such as headaches, nosebleeds, and respiratory infections; however, these were unrelated to the treatment. There were a greater number of subjects

Table 14. Summary of Adverse Events for Participants.

	Uridine Group ($N = 9$)	Placebo Group ($N = 8$)
Number of Adverse Events Reported	14	9
Number of Subjects with Adverse Events [1]	8	5
Number of Adverse Events by Relatedness to Treatment*		
Unrelated (Percentage)	9 (61.5%)	7 (77.8%)
Related (Percentage)	5 (35.7%)	2 (22.2%)

[1] Subjects who experience one or more adverse events are counted only once
* Percentages are based on number of adverse events reported for each treatment group

in the uridine than the placebo group that reported adverse events.

The most reported events for the uridine group were classified as gastrointestinal, which are known side effects of uridine. These events included upset stomach, vomiting, nausea, etc. Table 15 provides a classification of events by body system. These results suggest that participants safely tolerated treatment with uridine and there were no severe adverse events during the study.

Limitations and Future Considerations

Participant medications were not controlled for during the study, and this was a significant limitation of the study. Participants in the uridine and placebo group took different medications, including mood stabilizers, antidepressants, anti-anxiety medications, and medication for ADHD. Mood stabilizers, antidepressants, antipsychotics, and medications for anxiety could have a negative effect on depressive symptoms and neurocognitive test performance. In addition, certain medications could

Table 15. Adverse Events by Body System for Participants

System	Number of AEs*		Subjects with AEs	
	Uridine	Placebo	Uridine	Placebo
Constitutional	0 (0.0%)	1 (11.1%)	0 (0.0%)	1 (12.5%)
Hematologic	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Endocrine	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Psychiatric	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiovascular	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Genitourinary	1 (7.1%)	0 (0.0%)	1 (9.1%)	0 (0.0%)
Respiratory	2 (14.3%)	2 (22.2%)	2 (18.2%)	2 (25.0%)
Neurological	2 (14.3%)	4 (44.4%)	1 (9.1%)	3 (37.5%)
Gastrointestinal	5 (35.7%)	2 (22.2%)	5 (45.5%)	2 (25.0%)
Integumentary	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Musculoskeletal	1 (7.1%)	0 (0.0%)	1 (9.1%)	0 (0.0%)
HEENT	3 (21.4%)	0 (0.0%)	2 (18.2%)	0 (0.0%)
Overall	14	9		

* Percentages are based on number of AE reported for each treatment group.
AE: Adverse Event; HEENT: Head, eyes, ears, nose, and throat

have improved BD participants' cognitive test performance. For example, there were 6 participants taking lamotrigine, which has shown to increase working memory and verbal memory in adolescents with bipolar disorder after 14 weeks of treatment (Pavuluri et al., 2010). Additionally, there were 6 participants with ADHD, 3 of whom were taking medication for ADHD that may have improved participant performance on attention and other tasks. It would be critical to control for the use of medications in future studies of uridine in depressed participants with BD, especially the use of antidepressant mediations.

The small sample size significantly limits the findings of the study. Three participants were removed from the sample and 1 chose not to participate, which made the sample size even smaller. A larger sample size would improve statistical power and

increased generalizability. In particular, research is needed with larger participant pools at multiple locations to increase generalizability. In order to detect robust findings, a larger sample size would have been preferred. Another limitation to this study is the design, which may not have been sensitive to effects of the treatment and may not have accurately captured the biggest effect of uridine on depressive symptoms or neurocognitive performance. Rapid responses to pyrimidines to treat depression have been reported by Jensen et al. (2008) and Yoon et al. (2009). Jensen et al. (2008) reported a rapid-onset of treatment response to TAU within 4 weeks in a study of depressed rapid response following administration of cytidine as an adjunctive treatment to valproate during weeks 1 to 4 in bipolar depression throughout a 12-week trial.

To address potential problems with the study design, neuropsychological testing could be performed earlier in the study following 2 and 4 weeks of uridine administration. Neuropsychological performance could also be paired with another objective measure to increase the validity of results. For instance, neurocognitive testing could be performed in conjunction with functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS). Thus, participant neurocognitive performance could be analyzed with fMRI and MRS results to see if changes in the brain metabolites or blood flow are associated with changes in performance on neurocognitive tasks. Finally, future studies of uridine may benefit by shortening the length of the administration to 4 weeks and by focusing on repeated measurement during weeks 1 to 4.

Uridine levels have shown to be highest in the body for 2 hours after taking uridine orally. For participants who took study medication the morning prior to neuropsychological testing, uridine might have still been present in their bodies. For other subjects, the effect of uridine may not have lasted during neuropsychological testing.

Weight and metabolism of the participant could have also affected the how long the uridine stayed in the body/brain. Future studies might consider dosing participants with uridine based on their height and weight.

Additional changes to the design to decrease the effect of placebo response would be an especially important area of future research. Due to the difficulty in differentiating a treatment response in individuals with bipolar disorder, the use of placebo has been regarded as having a very important (yet complex) role in affective disorders research. Variables found to be associated with greater response to placebo in bipolar disorder trials include whether the person is in a mixed episode or first episode, whether he/she has rapid cycling; and whether the study employs a fixed-dose design (Vieta & Carne, 2005). Nierenberg et al. (2015) found that longer clinical trials and more severe illness reported at baseline also increased the risk of participants with BD responding to the placebo in randomized, double-blind treatment trials. These may be important variables to consider with placebo-controlled treatment trials for bipolar adolescents.

Participant adherence was another limitation of the study. It is unknown whether participants were actually taking study medication throughout the study. Even though participants and their parents reported taking the medication, it was not actually observed by the PI or Dr. Kondo. Furthermore, the only physical proof of treatment integrity in the study was participants keeping a medication log, bringing back unused medication to each weekly visit, and having it counted and recorded by staff. Future studies might employ medication dispensers that electronically record each time the study medication bottle is opened by the participant. This would dramatically increase future study costs, but it may also increase participant adherence and treatment integrity.

All mood measures and academic information were based on participant report.

This is a limitation, as many of the participants reported mood symptoms at the time of the study visit and may not have accurately reported for mood symptoms throughout the week. Future studies may consider use of electronic self-monitoring of mood throughout the study to help participants monitor bipolar symptoms frequently, which can be easily quantified to summarize symptoms throughout the week. These electronic mood trackers have been used in adult and adolescent studies of depression and bipolar disorder and technology in the form of applications on mobile phones and tablets, which are popular among youth.

The exclusion criterion of current substance use disorder may have led to a group of participants that were higher functioning academically and were exclusively in school or working. This may have implications for restriction in range of performance, and the neuropsychological domains may not be representative of the larger population of youth with BD. Specifically, substance use in BD is common and many youth with BD have reported using substances to cope with feelings and self-medicate. In fact, as high as 31% of youth with BD have been reported to have a comorbid substance use diagnosis (Frias, Palma, & Farriols, 2015). Substance use in adolescence is commonly associated with lower academic achievement and legal problems. Furthermore, use of substances over long periods has been associated with lower neuropsychological performance (Squeglia, Jacobus, & Tapert, 2009). Heavy alcohol use during adolescence can also decrease performance on memory, attention, spatial skills, and executive functioning.

Another limitation was the timing of the study, resulting in the inability to collect academic data. During the time period of the study, approximately half of the participants were enrolled during summer or when school was not in session. Additionally, 3 participants with BD and 6 participants were not attending school during the study.

Therefore, comparisons could not be made with regard to academic performance. Future studies might consider recruiting participants from a school district and collaborating with a school psychologists, teachers, and administrators to collect a variety of different types of academic data, including grades, questionnaires, or historical academic data.

Most of the participants with BD were able and willing to complete the testing; however, the amount of motivation and effort that participants put forth differed. Many of the participants were eager at the baseline visit to perform well and appeared to be highly motivated. After being exposed to all of the measures during the baseline, the tests were no longer novel and some of the participants with BD did not put forth the same amount of effort at the final visit. During the final administration of tests, many bipolar participants were not motivated and a few struggled to complete some of the tests, especially the CPT-3. At the final visit, one bipolar participant reported worry that the CPT-3 interval would never end and felt "trapped inside of it". Another participant stated upon completion of the CPT-3 at the final visit, that they would not return for another visit if they had to complete that test again. Both of these participants were in the uridine group. The level of effort and motivation by participants on testing, especially participants who struggled with testing was certainly a limitation of the study.

The level of involvement of participants and their families was tremendous; however, the time commitment may have led to increased investment and motivation, which is another limitation. Participants and their families came to the study participated in the informed consent process and were fully aware of the time and travel necessary to participate in the study. Several participants drove over 100 miles round-trip weekly to participate in the study for 6 weeks. The level of parent support/involvement in the study certainly had an effect on adolescent participants. Parents transported adolescents to the

visits, attended appointments, and discussed weekly changes in their child's mood. They coordinated appointments and helped the participants complete the study. This level of parent attention and support could be an alternate explanation for decrease in depression scores. Participants and their parents were highly motivated and desperately wanted to get better, were dedicated to the study, and were committed to improving regardless of whether they were assigned to the placebo or uridine condition.

Conclusion

Data from this study indicate that more research is needed regarding uridine as a treatment for depression in bipolar disorder. Three participants in the uridine group showed a treatment response, as did 4 participants in the placebo group. Uridine did not have any negative effects on neurocognitive performance, but it did not prove to have any benefits solely for the uridine group. Furthermore, there were no significant differences in neurocognitive performance between either the uridine or placebo groups, although participants with BD showed more impairment in attention, executive functioning, and processing speed than unaffected comparison participants. Academic experiences for participants with BD were different from comparison participants and included more academic difficulties, discontinuations, and transfers to new schools, programs, and classes. Participants who reported academic difficulties or received special education services performed lower on attention, working memory, executive functioning, and processing speed domains.

APPENDIX A

PARENT PERMISSION, CONSENT, AND ASSENT FORMS

Consent and Authorization Document

BACKGROUND

You are being asked to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you will take part in this research study.

The purpose of the study is to see if the investigational medication, uridine, reduces symptoms of depression and improves neuropsychological test performance in adolescents and young adults with bipolar disorder. Uridine is a naturally occurring chemical that is made by the human liver. Uridine is part of a family of compounds called pyrimidines and is normally involved in many of the body's processes, such as the use of energy by cells. Uridine is considered experimental because it has not been approved by the US Food and Drug Administration (FDA) to treat bipolar depression in adolescents.

The study you have been asked to take part in is being conducted at the same time with a randomized double-blind placebo-controlled clinical trial of uridine, IRB #00060256, "Placebo-Controlled Study of Uridine for Adolescent Bipolar Depression: a Magnetic Resonance Spectroscopy Study." That study has a placebo control (a dummy treatment that contains no active ingredient). All participants in that study will be randomly assigned to receive placebo or 500 mg of oral, twice daily uridine. Neither you nor the study team will know if you are receiving uridine or placebo. Since you are eligible for participation IRB #00060256, you are being offered participation in this study. All investigational procedures of uridine will take place under IRB #00060256. Placebo-controlled uridine will not be administered to you during this study.

In the past, uridine has been tested in adolescents with bipolar depression, as well as animal models of depression, both of which have shown good results. A Phase 1 study with adults resulted in no deaths or abnormal lab results. A Phase 2 study of adults with bipolar depression has also been completed. It showed that uridine was beneficial for adults with bipolar depression. There is also evidence that uridine increases cognitive and neuropsychological functioning in other medical conditions.

This study will use standard methods of assessing your mood, such as rating scales and questionnaires. This study will also use standard methods of neuropsychological performance that assess areas of thinking, like attention and working memory. Academic rating scales will be used to provide information about your current performance at school.

STUDY PROCEDURES

This section is designed to explain what you will do, undergo, and experience as part of taking part in this study.

Baseline Visit (~2 hours)
Once it is known that you are eligible for the study, we will schedule a baseline visit. The following will happen during the baseline visit:

1. We will briefly assess your mood to find out if you are still depressed and eligible to participate in the study.
2. You will be given several tests to assess your cognitive ability, attention, and working memory. Some of the tests will require you to sit at a computer and answer questions.
3. You will be given questionnaires for your teacher(s) to rate your current academic performance.

Final Visit (~2 hours)
1. We will perform the mood rating scales that were completed at the baseline visit.
2. You will take the same cognitive tests to assess your attention and working memory.
3. You will be given the same questionnaires for your teacher(s) to rate your current academic performance.

RISKS
- It is possible that your illness could worsen during the study. This could be related or unrelated to the study. Adolescents with bipolar disorder are at risk for depression, suicidal ideation, and suicide attempts as part of their illness. If your illness worsens to the point that the principal investigator considers you a danger to yourself or others, you will be hospitalized. If you are hospitalized, you will be withdrawn from the study. In the event of hospitalization, your insurance company will be responsible for the associated costs.
- The researchers will take precautions to safeguard your confidentiality, but it is possible that a breach of confidentiality could occur.

UNFORESEEABLE RISKS
In addition to the risks listed above, you may experience a previously unknown risk or side effect.

BENEFITS
We cannot promise any benefits to you from being in the study.

Other than direct benefits to you, there are possible indirect benefits:
- Results from the study will help doctors understand the way uridine affects young people with bipolar depression. This could help us improve treatment for adolescents and young adults with bipolar disorder.

ALTERNATIVE PROCEDURES
You may choose to not participate in this study. If you do not want to take part in the study, there are other choices for you. If you decide not to participate in this study, it will not affect your participation in IRB # 00060256.

CONFIDENTIALITY
Results of this study may be published, but your identity will not appear in any such publication. We will keep all research records that identify you private to the extent allowed by law. Records about you will be kept in locked filing cabinets, in offices that only the research team has access to. Study records will also be stored on computers protected with passwords. Only those working on study will be allowed access to your information. The University of Utah's Institutional Review Board (IRB) is responsible for making sure that researchers follow federal laws to protect human subjects. Staff of the IRB may at any time, ask to look at our records to make sure the research staff is following the laws to protect you. We will do everything we can to keep your records private, but cannot guarantee this.

When you agree to take part in this study, you are also agreeing to share your health information for the life of this study or in some instances for an indefinite time. Do not agree to take part if you don't want us to share your health information. Taking part is voluntary. You have the choice to take part or not. You must understand that if you decide not to take part that it will not change any part of the standard health care you will otherwise receive. Also remember, you can leave the research study at any time. However, we will be able to use any of your health information that we collected for the research.

If we believe there is a danger of harm to you or to others, the principal investigator will inform you directly. If you tell us you are being physically or sexually abused, the researchers are required by law to inform the appropriate government agency.

PERSON TO CONTACT
If you have questions, complaints or concerns about this study, you can contact Rebekah Huber at (801) 587-1439. The line is connected to a confidential voicemail. You may also call Dr. Kondo at any time if you have concerns about IRB # 00060256. He can be reached by calling the University Neuropsychiatric Institute hospital operator 24 hours per day at (801) 583-2500. The operator can page Dr. Kondo at any time. If Dr. Kondo is out-of-town, the hospital operator will know which study physician is on-call and can reach that doctor 24 hours per day. If you think you may have been injured from being in this study, please call Rebekah Huber at (385) 228-3560 or Dr. Kondo at: (801) 581-5413 or (801) 583-2500.

Institutional Review Board: Contact the Institutional Review Board (IRB) if you have questions regarding your rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at (801) 581-3655 or by e-mail at irb@hsc.utah.edu.

Research Participant Advocate: You may also contact the Research Participant Advocate (RPA) by phone at (801) 581-3803 or by email at participant.advocate@hsc.utah.edu.

RIGHT OF INVESTIGATOR TO WITHDRAW
The investigator can withdraw you from the study without your approval. Possible reasons for withdrawal include: inability to comply with the study protocol.

COSTS AND COMPENSATION TO PARTICIPANTS
The study visits and evaluation will be provided to you at no cost.

For completion of each visit, you will receive compensation as outlined below:
- Baseline visit: $25
- Follow-up visit: $25

NEW INFORMATION
Sometimes during the course of a research study, new information becomes available about the treatment that is being studied. If new information comes out about uridine over the course of this study, your principal investigator will tell you about it and discuss with you whether or not you want to continue in the study.

NUMBER OF PARTICIPANTS
We expect to enroll 60 participants in this study, 40 participants with bipolar disorder and 20 participants without bipolar disorder, all at the University of Utah.

AUTHORIZATION FOR USE OF YOUR PROTECTED HEALTH INFORMATION
Signing this document means you allow us, the researchers in this study, and others working with us to use some information about your health for this research study.

This is the information we will use and include in our research records:

- Demographic and identifying information like name, date of birth, address, and telephone number.
- Related medical information about you like family psychiatric and medical history, current and past medications and therapies, and information from physical exams.
- All tests and procedures that will be done in the study.

How we will protect and share your information:

We will do everything we can to keep your information private but we cannot guarantee this. Study information will be kept in a secured manner and electronic records will be password protected. Study information may be stored with other information in your medical record. Other doctors, nurses, and third parties (like insurance companies) may be able to see this information as part of the regular treatment, payment, and health care operations of the hospital. We may also need to disclose information if required by law.

In order to conduct this study and make sure it is conducted as described in this form, the research records may be used and reviewed by others who are working with us on this research:

- Authorized members of the research team

NEW INFORMATION
Sometimes during the course of a research study, new information becomes available about the treatment that is being studied. If new information comes out about uridine over the course of this study, your principal investigator will tell you about it and discuss with you whether or not you want to continue in the study.

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AUTHORIZATION FOR USE OF YOUR PROTECTED HEALTH INFORMATION
Signing this document means you allow us, the researchers in this study, and others working with us to use some information about your health for this research study.

This is the information we will use and include in our research records:

- Demographic and identifying information like name, date of birth, address, and telephone number.
- Related medical information about you like family psychiatric and medical history, current and past medications and therapies, and information from physical exams.
- All tests and procedures that will be done in the study.

How we will protect and share your information:

We will do everything we can to keep your information private but we cannot guarantee this. Study information will be kept in a secured manner and electronic records will be password protected. Study information may be stored with other information in your medical record. Other doctors, nurses, and third parties (like insurance companies) may be able to see this information as part of the regular treatment, payment, and health care operations of the hospital. We may also need to disclose information if required by law.

In order to conduct this study and make sure it is conducted as described in this form, the research records may be used and reviewed by others who are working with us on this research:

- Authorized members of the research team
- The University of Utah's Institutional Review Board (IRB), who reviews research involving people to make sure the study protects your rights.

If we share your information with groups outside of the University of Utah, we will not share your name or identifying information. We will label your information with a code number, so they will not know your identity.

If you do not want us to use information about your health, you should not be part of this research. If you choose not to participate, you can still receive health care services at University of Utah Sciences Center.

What if I decide to Not Participate after I sign the Consent and Authorization Form?

You can tell us anytime that you do not want to be in this study and do not want us to use your health information. You can also tell us in writing. You must either give your revocation in person to the Principal Investigator or the Principal Investigator's staff, or mail it to Rebekah Huber at: The Brain Institute, 383 Colorow Dr., Salt Lake City, UT 84108. If you change your mind, we will not be able to collect new information about you, and you will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research.

This authorization does not have an expiration date.

You have a right to information used to make decisions about your health care. However, your information from this study will not be available during the study; it will be available after the study is finished.

CONSENT

I confirm that I have read this consent and authorization document and have had the opportunity to ask questions. I will be given a signed copy of the consent and authorization form to keep.

I agree to take part in this research study and authorize you to use and disclose health information about me for this study, as you have explained in this document.

_____
Participant's Name

_____ _____
Participant's Signature Date

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Signature of Person Obtaining Authorization and Consent Date

Parental Permission and Authorization Document

BACKGROUND

Your child is being asked to take part in a research study. Before you decide whether or not to allow your child to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you will allow your child to take part in this research study.

The purpose of the study is to see if the investigational medication, uridine, reduces symptoms of depression and improves neuropsychological test performance in adolescents with bipolar disorder. Uridine is a naturally occurring chemical that is made by the human liver. Uridine is part of a family of compounds called pyrimidines and is normally involved in many of the body's processes, such as the use of energy by cells. Uridine is considered experimental because it has not been approved by the US Food and Drug Administration (FDA) to treat bipolar depression in adolescents.

The study your child has been asked to take part in is being conducted concurrently with a randomized double-blind placebo-controlled clinical trial of uridine, IRB #00060256, "Placebo-Controlled Study of Uridine for Adolescent Bipolar Depression: a Magnetic Resonance Spectroscopy Study." That study has a placebo control (a dummy treatment that contains no active ingredient). All participants in that study will be randomly assigned to receive placebo or 500 mg of oral, twice daily uridine. Neither you nor the study team will know if your child is receiving uridine or placebo. Since you are eligible for participation IRB #00060256, you are being offered participation in this study. All investigational procedures of uridine will take place under IRB #00060256. Placebo-controlled uridine will not be administered to your child during this study.

In the past, uridine has been tested in adolescents with bipolar depression, as well as animal models of depression, both of which have shown good results. A Phase 1 study with adults resulted in no deaths or abnormal lab results. A Phase 2 study of adults with bipolar depression has also been completed. It showed that uridine was beneficial for adults with bipolar depression. There is also evidence that uridine increases cognitive and neuropsychological functioning in other medical conditions.

This study will use standard methods of assessing your child's mood, such as rating scales and questionnaires. This study will also use standard methods of neuropsychological performance that assess areas of thinking, like attention and working memory. Academic rating scales will be used to provide information about your child's current performance at school.

STUDY PROCEDURES

This section is designed to explain what your child will do, undergo, and experience as part of taking part in this study.

Baseline Visit: (~2 hours)
Once it is known that your child is eligible for the study, we will schedule a baseline visit. The following will happen during the baseline visit:

1. We will briefly assess your child's mood to find out if they are still depressed and eligible to participate in the study.
2. Your child will be given several tests to assess their cognitive ability, attention, and working memory. Some of the tests will require your child to sit at a computer and answer questions.
3. Your child will be given questionnaires for their teacher(s) to rate their current academic performance.

Final Visit: (~2 hours)
1. We perform the rating scales that were completed at the baseline visit.
2. Your child will be given the same cognitive tests to assess their attention and working memory.
3. You child will be given the same questionnaires for their teacher(s) to rate their current academic performance.

RISKS
- It is possible that your child's illness could worsen during the study. This could be related or unrelated to the study. Adolescents with bipolar disorder are at risk for depression, suicidal ideation, and suicide attempts as part of their illness. If your child's illness worsens to the point that the principal investigator considers them a danger to themselves or others, they will be hospitalized. If your child is hospitalized, they will be withdrawn from the study. In the event of hospitalization, you or your child's insurance company will be responsible for the associated costs.
- The researchers will take precautions to safeguard your child's confidentiality, but it is possible that a breach of confidentiality could occur.

UNFORESEEABLE RISKS
In addition to the risks listed above, your child may experience a previously unknown risk or side effect.

BENEFITS
We cannot promise any benefits to your child from being in the study. However, there are some possible benefits to your child if she participates in this study:

- We hope that your child will benefit, but this cannot be guaranteed.

Other than direct benefits to your child, there are possible indirect benefits:

- Results from the study will help doctors understand the way uridine affects young people with bipolar depression. This could help us improve treatment for adolescents and young adults with bipolar disorder.

ALTERNATIVE PROCEDURES

You may choose to not have your child participate in this study. If you or your child does not want to take part in the study, there are other choices for your child. If you decide not to participate in this study, it will not affect your child's participation in IRB # 00060256.

CONFIDENTIALITY

Results of this study may be published, but your child's identity will not appear in any such publication. We will keep all research records that identify your child private to the extent allowed by law. Records about your child will be kept in locked filing cabinets, in offices that only the research team has access to. Study records will also be stored on computers protected with passwords. Only those working on study will be allowed access to your child's information. The University of Utah's Institutional Review Board (IRB) is responsible for making sure that researchers follow federal laws to protect human subjects. Staff of the IRB may at any time, ask to look at our records to make sure the research staff is following the laws to protect your child. We will do everything we can to keep your child's records private, but cannot guarantee this.

When you agree to take part in this study, you are also agreeing to share your child's health information for the life of this study or in some instances for an indefinite time. Do not agree to take part if you don't want us to share your child's health information. Taking part is voluntary. You have the choice to take part or not. You must understand that if you decide not to take part that it will not change any part of the standard health care your child will otherwise receive. Also remember, your child can leave the research study at any time. However, we will be able to use any of your child's health information that we collected for the research.

If we believe there is a danger of harm to your child or to others, the principal investigator will inform you directly. If your child tells us they are being physically or sexually abused, the researchers are required by law to inform the appropriate government agency.

PERSON TO CONTACT

If you have questions, complaints or concerns about this study, you can contact Rebekah Huber at (801) 587-1439. The line is connected to a confidential voicemail. You may also call Dr. Kondo at any time if you have concerns about IRB # 00060256. He can be reached by calling the University Neuropsychiatric Institute hospital operator 24 hours per day at (801) 583-2500. The operator can page Dr. Kondo at any time. If Dr. Kondo is out-of-town, the hospital operator will know which study physician is on-call and can reach that doctor 24 hours per day. If you think you may have been injured from being in this study, please call Rebekah Huber at (385) 228-3560 or Dr. Kondo at: (801) 581-5413 or (801) 583-2500.

Institutional Review Board: Contact the Institutional Review Board (IRB) if you have questions regarding your child's rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at (801) 581-3655 or by e-mail at irb@hsc.utah.edu.

Research Participant Advocate: You may also contact the Research Participant Advocate (RPA) by phone at (801) 581-3803 or by email at participant.advocate@hsc.utah.edu.

FOOTER FOR IRB USE ONLY
Version: B0215

RESEARCH-RELATED INJURY
If your child is injured from being in this study, medical care is available at the University of Utah, as it is to all sick or injured people. The University of Utah has not set aside any money to pay the costs for such care. The University will work with you to address costs from injuries. Costs would be charged to you or your insurance company (if you have insurance) or other third party (if applicable), to the extent those parties are responsible for paying for medical care your child receives. Since this is a research study, some health insurance plans may not pay for the costs. By signing this consent form you are not giving up your right to pursue legal action against any parties involved with this research.

The University of Utah is a part of the government. If your child is injured in this study, and you want to sue the University or the doctors, nurses, students, or other people who work for the University, special laws may apply. The Governmental Immunity Act of Utah is a law that controls when a person needs to bring a claim against the government, and limits the amount of money a person may recover. See sections 63G -7-101 to -904 of the Utah Code.

VOLUNTARY PARTICIPATION
If you decide to allow your child to take part you are still free to withdraw your child at any time and without giving a reason. Refusal to allow your child to participate or the decision to withdraw your child from this study will involve no penalty or loss of benefits to which your child is otherwise entitled. If your child doesn't take part, your child can still receive all standard care that is available. This will not affect the relationship you or your child has with your child's doctor or other staff, nor decrease the standard of care that your child receives as a patient. If you decide to stop your child from being in this study, please let the research doctor know. That way you can find out what should be done about your child's medical care outside of the study.

RIGHT OF INVESTIGATOR TO WITHDRAW
The investigator can withdraw your child from the study without your approval. Possible reasons for withdrawal include: inability to comply with the study protocol, two consecutive missed weekly appointments, or worsening of your child's condition that requires hospitalization for safety. The principal investigator may also terminate your child's participation if they feel that the study medication as part of IRB #00060256 is making your child worse.

COSTS AND COMPENSATION TO PARTICIPANTS
The study visits and evaluations will be provided to your child at no cost. All other costs will be billed to you and your insurance company in the usual way, as part of your standard care. Medications that your child takes for medical conditions other than bipolar depression are not covered by the study. Your child's prescriptions for mood stabilization will also not be covered by the study.

For completion of each visit, your child will receive compensation as outlined below:

Study Week	Screen	0	1	2	3	4	5	6	8
Subject payment		$25						$25	
Total compensation									$50

NEW INFORMATION
Sometimes during the course of a research study, new information becomes available about the treatment that is being studied. If new information comes out about uridine over the course of this study, your child's research doctor will tell you about it and discuss with you whether or not you want your child to continue in the study.

NUMBER OF PARTICIPANTS
We expect to enroll 60 participants in this study, 40 participants with bipolar disorder and 20 participants without bipolar disorder, all at the University of Utah.

AUTHORIZATION FOR USE OF YOUR PROTECTED HEALTH INFORMATION
Signing this document means you allow us, the researchers in this study, and others working with us to use some information about your health for this research study.

This is the information we will use and include in our research records:

- Demographic and identifying information like name, date of birth, address, and telephone number.
- Related medical information about you like family psychiatric and medical history, current and past medications and therapies, and information from physical exams.
- All tests and procedures that will be done in the study.

How we will protect and share your information:

We will do everything we can to keep your information private but we cannot guarantee this. Study information will be kept in a secured manner and electronic records will be password protected. Study information may be stored with other information in your medical record. Other doctors, nurses, and third parties (like insurance companies) may be able to see this information as part of the regular treatment, payment, and health care operations of the hospital. We may also need to disclose information if required by law.

In order to conduct this study and make sure it is conducted as described in this form, the research records may be used and reviewed by others who are working with us on this research:

- Authorized members of the research team
- The University of Utah's Institutional Review Board (IRB), who reviews research involving people to make sure the study protects your rights.

If we share your information with groups outside of the University of Utah, we will not share your name or identifying information. We will label your information with a code number, so they will not know your identity.

If you do not want us to use information about your health, you should not be part of this research. If you choose not to participate, you can still receive health care services at University of Utah Sciences Center.

What if I decide to Not Participate after I sign the Consent and Authorization Form?

You can tell us anytime that you do not want to be in this study and do not want us to use your health information. You can also tell us in writing. You must either give your revocation in person to the Principal Investigator or the Principal Investigator's staff, or mail it to Rebekah Huber at: The Brain Institute, 383 Colorow Dr., Salt Lake City, UT 84108. If you change your mind, we will not be able to collect new information about you, and you will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research.

This authorization does not have an expiration date.

You have a right to information used to make decisions about your child's health care. However, your child's information from this study will not be available during the study; it will be available after the study is finished.

CONSENT:

I confirm that I have read this parental permission document and have had the opportunity to ask questions. I will be given a signed copy of the parental permission form to keep.
I agree to allow my child to participate in this research study and authorize you to use and disclose health information about my child for this study, as you have explained in this document.

_____
Child's Name

_____
Parent/Guardian's Name

_____ _____
Parent/Guardian's Signature Date

_____
Relationship to Child for Parent/Guardian

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Signature of Person Obtaining Authorization and Consent Date

Assent to Participate in a Research Study

Who are we and what are we doing?
We are from the Brain Institute of the University of Utah. We would like to ask if you would like to be in a research study. A research study is a way to find out new information about something.

Why are we asking you to be in this research study?
We are trying to find out if the investigational drug uridine can help depressed adolescents and young adults with bipolar disorder, when compared to taking a placebo. A placebo is a substance that contains no active ingredient, but looks exactly like the real drug. The reason for asking you to participate is because you have bipolar disorder and are currently depressed and you are already taking part in in IRB #00060256.

This study will use questionnaires and tests of attention and memory to understand more about bipolar disorder. We will compare the results of youth with bipolar disorder to the results of youth without bipolar disorder.

Uridine occurs naturally in the body and is made in the liver. It plays a part in many processes and chemical reactions in the body. Some patients with medical conditions other than bipolar disorder have been treated with uridine for more than 20 years. Uridine has been shown to help people with memory cognition.

What happens in the research study?
If you decide to be in this research study and your parent or guardian agrees, this is what will happen:

- We will ask you questions to make sure that bipolar disorder is the correct diagnosis, and to see if you are depressed.
- We will ask you to complete learning, attention, and memory tasks at the beginning and the end of the study. Some of these tasks will be done on a computer.
- We will give your teacher checklists to rate your current academic performance.

The research study may be stopped before you finish it. If this happens, you will be told why. Some of the reasons it may be stopped early are:

- Feeling worse and the principal investigator determines it is unsafe for you to continue in the study.
-

You may also be asked to stop being in the study if you are not following the directions from the principal investigator.

Will any part of the research study hurt you?
The tests are considered painless

Will the research study help you or anyone else?
There may be benefits to society, called "indirect benefits." The study may help doctors understand bipolar disorder, so that future patients will receive better treatment. This study may help doctors understand if uridine works for adolescents with bipolar disorder.

Who will see the information about you?
Only the researchers or others who are doing their jobs will be able to see the information about you from this research study. We will talk about this information with you, your doctors, and your parents. All of the information we collect about you will be kept in a locked cabinet or on computers that are protected by passwords. If you tell us that you want to hurt yourself, we will tell other adults about it so that we can help you feel better. We have to disclose information to those necessary if you tell us that you have been abused or intend to hurt others or yourself.

What if you have any questions about the research study?
You can ask any question you want about the study. If you have a question later that you didn't think of now, you can call me (Rebekah Huber) or ask me next time. You may call me to ask questions about your disease or treatment. My phone number is: (801)587-1439 or (385) 228-3560. You can also call Dr. Kondo at (801) 258-1659. He can be paged by contacting the hospital operator, at (801) 583-2500, and someone will answer 24 hours per day, including weekends and holidays.

Do you have to be in the research study?
You do not have to be in this study if you don't want to. Being in this study is up to you. No one will be upset if you don't want to do it. Even if you say yes now, you can change your mind later and tell us you want to stop. Please talk this over with your parents or guardians before you decide whether or not to participate. We will also ask your parents or guardians to give their permission for you to take part in this study. But even if your parents or guardians say "yes," you can still say "no" and decide not to do this.

There are alternatives to being in this study. You and your family can choose to not participate.

Agreeing to be in the study
I was able to ask questions about this study. Signing my name at the bottom means that I agree to be in this study. My parent or guardian and I will be given a copy of this form after I have signed it.

_____
Printed Name

_____ _____
Sign your name on this line Date

Printed Name of Person Obtaining Assent

Signature of Person Obtaining Assent Date

The following should be completed by the study member conducting the assent process if the participant agrees to be in the study. Initial the appropriate selection:

_____ The participant is capable of reading the assent form and has signed above as documentation of assent to take part in this study.

_____ The participant is not capable of reading the assent form, but the information was verbally explained to him/her. The participant signed above as documentation of assent to take part in this study.

Consent and Authorization Document

You are being asked to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you will take part in this research study.

The purpose of the study is to see if the investigational medication, uridine, reduces symptoms of depression and improves neuropsychological test performance in adolescents and young adults with bipolar disorder. Uridine is a naturally occurring chemical that is made by the human liver. Uridine is part of a family of compounds called pyrimidines and is normally involved in many of the body's processes, such as the use of energy by cells.

The study you have been asked to take part in is being conducted at the same time with a randomized double-blind placebo-controlled clinical trial of uridine, IRB #00060256, "Placebo-Controlled Study of Uridine for Adolescent Bipolar Depression: a Magnetic Resonance Spectroscopy Study." Since you are eligible for participation IRB #00060256, you are being offered participation in this study. All investigational procedures of uridine will take place under IRB #00060256. You are being asked to be in the study because you do not have bipolar disorder. You will *not* be given uridine. Healthy individuals are included in this study to use as a comparison group to the study subjects who have bipolar disorder.

This study will use standard methods of assessing your mood, such as rating scales and questionnaires. This study will also use standard methods of neuropsychological performance that assess areas of thinking, like attention and working memory. Academic rating scales will be used to provide information about your current performance at school.

STUDY PROCEDURES
This section is designed to explain what you will do, undergo, and experience as part of taking part in this study.

The study will take place during two study visits. The study will last a total of 8 weeks. This study will use standard methods of assessing your mood, such as rating scales and questionnaires. At the baseline and final study visits, you will also be given cognitive assessments and academic checklists.

If you decide to take part in this research study, the following details what will occur:

Baseline Visit (~2 hours)
Once it is known that you are eligible for the study, we will schedule a baseline visit. The following will happen during the baseline visit:

1. We will briefly assess your mood to make sure you are eligible to participate in the study.

2. You will be given several tests to assess your cognitive ability, attention, and working memory. Some of the tests will require you to sit at a computer and answer questions.
3. You will be given questionnaires for your teacher(s) to rate your current academic performance.

Final Visit (~2 hours)

1. We will perform the mood rating scales that were completed at the baseline visit.
2. You will take the same cognitive tests to assess your attention and working memory.
3. You will be given questionnaires for your teacher(s) to rate your current academic performance.

RISKS

- The researchers will take precautions to safeguard your confidentiality, but it is possible that a breach of confidentiality could occur.

UNFORESEEABLE RISKS

In addition to the risks listed above, you may experience a previously unknown risk or side effect.

BENEFITS

Participating in the study will not directly benefit you, but there is the possible indirect benefit that the results from this study will help doctors understand more about young people with bipolar depression.

ALTERNATIVE PROCEDURES

You may choose to not participate in this study.

CONFIDENTIALITY

Results of this study may be published, but your identity will not appear in any such publication. We will keep all research records that identify you private to the extent allowed by law. Records about you will be kept in locked filing cabinets, in offices that only the research team has access to. Study records will also be stored on computers protected with passwords. Only those working on study will be allowed access to your information. The University of Utah's Institutional Review Board (IRB) is responsible for making sure that researchers follow federal laws to protect human subjects. Staff of the IRB may at any time, ask to look at our records to make sure the research staff is following the laws to protect you. We will do everything we can to keep your records private, but cannot guarantee this.

When you agree to take part in this study, you are also agreeing to share your heath information for the life of this study or in some instances for an indefinite time. Do not agree to take part if you don't want us to share your health information. Taking part is voluntary. You have the choice to take part or not. You must understand that if you decide not to take part that it will not change any part of the standard health care you will otherwise receive. Also remember, you can leave the research study at any time. However, we will be able to use any of your health information that we collected for the research.

If we believe there is a danger of harm to you or to others, the principal investigator will inform you directly. If you tell us you are being physically or sexually abused, the researchers are required by law to inform the appropriate government agency.

PERSON TO CONTACT

If you have questions, complaints or concerns about this study, you can contact Rebekah Huber at (801) 587-1439. The line is connected to a confidential voicemail. You may also call Dr. Kondo at any time if you have concerns about IRB # 00060256. He can be reached by calling the University Neuropsychiatric Institute hospital operator 24 hours per day at (801) 583-2500. The operator can page Dr. Kondo at any time. If Dr. Kondo is out-of-town, the hospital operator will know which study physician is on-call and can reach that doctor 24 hours per day. If you think you may have been injured from being in this study, please call Rebekah Huber at (385) 228-3560 or Dr. Kondo at: (801) 581-5413 or (801) 583-2500.

Institutional Review Board: Contact the Institutional Review Board (IRB) if you have questions regarding your rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at (801) 581-3655 or by e-mail at irb@hsc.utah.edu.

Research Participant Advocate: You may also contact the Research Participant Advocate (RPA) by phone at (801) 581-3803 or by email at participant.advocate@hsc.utah.edu.

RESEARCH-RELATED INJURY

If you are injured from being in this study, medical care is available at the University of Utah, as it is to all sick or injured people. The University of Utah has not set aside any money to pay the costs for such care. The University will work with you to address costs from injuries. Costs would be charged to you or your insurance company (if you have insurance) or other third party (if applicable), to the extent those parties are responsible for paying for medical care you receive. Since this is a research study, some health insurance plans may not pay for the costs. By signing this consent form you are not giving up your right to pursue legal action against any parties involved with this research.

The University of Utah is a part of the government. If you are injured in this study, and you want to sue the University or the doctors, nurses, students, or other people who work for the University, special laws may apply. The Governmental Immunity Act of Utah is a law that controls when a person needs to bring a claim against the government, and limits the amount of money a person may recover. See sections 63G -7-101 to -904 of the Utah Code.

VOLUNTARY PARTICIPATION

If you decide to take part, you are still free to withdraw at any time and without giving a reason. The decision to withdraw yourself from this study will involve no penalty or loss of benefits to which you are otherwise entitled. If you do not take part, you can still receive all standard care that is available. If you decide to stop being in this study, please let the principal investigator know.

RIGHT OF INVESTIGATOR TO WITHDRAW
The investigator can withdraw you from the study without your approval. Possible reasons for withdrawal include: inability to comply with the study protocol.

COSTS AND COMPENSATION TO PARTICIPANTS
The study visits and evaluation will be provided to you at no cost.

For completion of each visit, you will receive compensation as outlined below:
- Baseline visit: $25
- Follow-up visit: $25

NEW INFORMATION
Sometimes during the course of a research study, new information becomes available about the treatment that is being studied. If new information comes out about uridine over the course of this study, your principal investigator will tell you about it and discuss with you whether or not you want to continue in the study.

NUMBER OF PARTICIPANTS
We expect to enroll 60 participants in this study, 40 participants with bipolar disorder and 20 participants without bipolar disorder, all at the University of Utah.

AUTHORIZATION FOR USE OF YOUR PROTECTED HEALTH INFORMATION
Signing this document means you allow us, the researchers in this study, and others working with us to use some information about your health for this research study.

This is the information we will use and include in our research records:

- Demographic and identifying information like name, date of birth, address, and telephone number.
- Related medical information about you like family psychiatric and medical history, current and past medications and therapies, and information from physical exams.
- All tests and procedures that will be done in the study.

How we will protect and share your information:

We will do everything we can to keep your information private but we cannot guarantee this. Study information will be kept in a secured manner and electronic records will be password protected. Study information may be stored with other information in your medical record. Other doctors, nurses, and third parties (like insurance companies) may be able to see this information as part of the regular treatment, payment, and health care operations of the hospital. We may also need to disclose information if required by law.

In order to conduct this study and make sure it is conducted as described in this form, the research records may be used and reviewed by others who are working with us on this research:

- Authorized members of the research team

- The University of Utah's Institutional Review Board (IRB), who reviews research involving people to make sure the study protects your rights.

If we share your information with groups outside of the University of Utah, we will not share your name or identifying information. We will label your information with a code number, so they will not know your identity.

If you do not want us to use information about your health, you should not be part of this research. If you choose not to participate, you can still receive health care services at University of Utah Sciences Center.

What if I decide to Not Participate after I sign the Consent and Authorization Form?

You can tell us anytime that you do not want to be in this study and do not want us to use your health information. You can also tell us in writing. . You must either give your revocation in person to the Principal Investigator or the Principal Investigator's staff, or mail it to Rebekah Huber at: The Brain Institute, 383 Colorow Dr., Salt Lake City, UT 84108. If you change your mind, we will not be able to collect new information about you, and you will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research.

This authorization does not have an expiration date.

You have a right to information used to make decisions about your health care. However, your information from this study will not be available during the study; it will be available after the study is finished.

CONSENT
I confirm that I have read this consent and authorization document and have had the opportunity to ask questions. I will be given a signed copy of the consent and authorization form to keep.

I agree to take part in this research study and authorize you to use and disclose health information about me for this study, as you have explained in this document.

_____
Participant's Name

_____ _____
Participant's Signature Date

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Signature of Person Obtaining Authorization and Consent Date

Parental Permission and Authorization Document

Your child is being asked to take part in a research study. Before you decide whether or not to allow your child to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you will allow your child take part in this research study.

The purpose of the study is to see if the investigational medication, uridine, reduces symptoms of depression and improves neuropsychological test performance in adolescents and young adults with bipolar disorder. Uridine is a naturally occurring chemical that is made by the human liver. Uridine is part of a family of compounds called pyrimidines and is normally involved in many of the body's processes, such as the use of energy by cells.

The study your child has been asked to take part in is being conducted concurrently with a randomized double-blind placebo-controlled clinical trial of uridine, IRB #00060256, "Placebo-Controlled Study of Uridine for Adolescent Bipolar Depression: a Magnetic Resonance Spectroscopy Study." All investigational procedures of uridine will take place under IRB #00060256. Your child is being asked to be in the study because he/she does not have bipolar disorder. Since you child is eligible for participation IRB #00060256, he or she is being offered participation in this study. Your child will *not* be given uridine. Healthy individuals are included in this study to use as a comparison group to the study subjects who have bipolar disorder.

This study will use standard methods of assessing your child's mood, such as rating scales and questionnaires. This study will also use standard methods of neuropsychological performance that assess areas of thinking, like attention and working memory. Academic rating scales will be used to provide information about your child's current performance at school.

STUDY PROCEDURES
This section is designed to explain what your child will do, undergo, and experience as part of taking part in this study.

The study will take place during three study visits. The study will last a total of 8 weeks. At the screening visit, your child will be evaluated to determine if he/she has any psychiatric or medical illnesses. At the baseline and final study visits, your child will be given cognitive assessments and academic checklist.

If you and your child decide to take part in this research study, the following details what will occur:

Baseline Visit: (~2 hours)
Once it is known that your child is eligible for the study, we will schedule a baseline visit. The following will happen during the baseline visit:

1. We will briefly assess your child again to find out if his/her mood has significantly changed since the first time we saw him/her.
2. You child will be given several tests to assess his/her cognitive ability, attention, and working memory. Some of the tests will require your child to sit at a computer and answer questions.
3. Your child will be given questionnaires for his/her teacher(s) to rate his/her current academic performance.

Final Visit: (~2 hours)

1. We will perform the mood rating scales that were completed at the baseline visit..
2. You child will be given the same cognitive tests to assess attention and working memory.
3. You child will be given the same questionnaires for his/her teacher(s) to rate current academic performance.

RISKS

- The researchers will take precautions to safeguard your child's confidentiality, but it is possible that a breach of confidentiality could occur.

UNFORESEEABLE RISKS

In addition to the risks listed above, your child may experience a previously unknown risk or side effect.

BENEFITS

Participating in the study will not directly benefit your child, but there is the possible indirect benefit that the results from this study will help doctors understand more about young people with bipolar depression.

ALTERNATIVE PROCEDURES

You may choose to not allow your child to participate in this study.

CONFIDENTIALITY

Results of this study may be published, but your child's identity will not appear in any such publication. We will keep all research records that identify your child private to the extent allowed by law. Records about your child will be kept in locked filing cabinets, in offices that only the research team has access to. Study records will also be stored on computers protected with passwords. Only those working on study will be allowed access to your child's information. The University of Utah's Institutional Review Board (IRB) is responsible for making sure that researchers follow federal laws to protect human subjects. Staff of the IRB may at any time, ask to look at our records to make sure the research staff is following the laws to protect your child. We will do everything we can to keep your child's records private, but cannot guarantee this.

When you agree to take part in this study, you are also agreeing to share your child's heath information for the life of this study or in some instances for an indefinite time. Do not agree to take part if you don't want us to share your child's health information. Taking part is voluntary. You have the choice to take part or not. You must understand that if you decide not to take part

that it will not change any part of the standard health care your child will otherwise receive. Also remember, your child can leave the research study at any time. However, we will be able to use any of your child's health information that we collected for the research.

If we believe there is a danger of harm to your child or to others, a study doctor will inform you directly. If your child tells us they are being physically or sexually abused, the researchers are required by law to inform the appropriate government agency.

PERSON TO CONTACT

If you have questions, complaints or concerns about this study, you can contact Rebekah Huber at (801) 587-1439. The line is connected to a confidential voicemail. You may also call Dr. Kondo at any time if you have concerns about IRB # 00060256. He can be reached by calling the University Neuropsychiatric Institute hospital operator 24 hours per day at (801) 583-2500. The operator can page Dr. Kondo at any time. If Dr. Kondo is out-of-town, the hospital operator will know which study physician is on-call and can reach that doctor 24 hours per day. If you think you may have been injured from being in this study, please call Rebekah Huber at (385) 228-3560 or Dr. Kondo at: (801) 581-5413 or (801) 583-2500.

Institutional Review Board: Contact the Institutional Review Board (IRB) if you have questions regarding your child's rights as a research participant. Also, contact the IRB if you have questions, complaints or concerns which you do not feel you can discuss with the investigator. The University of Utah IRB may be reached by phone at (801) 581-3655 or by e-mail at irb@hsc.utah.edu.

Research Participant Advocate: You may also contact the Research Participant Advocate (RPA) by phone at (801) 581-3803 or by email at participant.advocate@hsc.utah.edu.

RESEARCH-RELATED INJURY

If your child is injured from being in this study, medical care is available at the University of Utah, as it is to all sick or injured people. The University of Utah has not set aside any money to pay the costs for such care. The University will work with you to address costs from injuries. Costs would be charged to you or your insurance company (if you have insurance) or other third party (if applicable), to the extent those parties are responsible for paying for medical care your child receives. Since this is a research study, some health insurance plans may not pay for the costs. By signing this consent form you are not giving up your right to pursue legal action against any parties involved with this research.

The University of Utah is a part of the government. If your child is injured in this study, and you want to sue the University or the doctors, nurses, students, or other people who work for the University, special laws may apply. The Governmental Immunity Act of Utah is a law that controls when a person needs to bring a claim against the government, and limits the amount of money a person may recover. See sections 63G -7-101 to -904 of the Utah Code.

VOLUNTARY PARTICIPATION

If you decide to allow your child to take part you are still free to withdraw your child at any time and without giving a reason. Refusal to allow your child to participate or the decision to withdraw

your child from this study will involve no penalty or loss of benefits to which your child is otherwise entitled. If you decide to stop your child from being in this study, please let the research doctor know.

RIGHT OF INVESTIGATOR TO WITHDRAW
The investigator can withdraw your child from the study without your approval. Possible reasons for withdrawal include: a positive pregnancy test or a positive drug screen.

COSTS AND COMPENSATION TO PARTICIPANTS
The study doctor visits and brain scan will be provided to your child at no cost.

For completion of each visit, your child will receive compensation as outlined below:
- Baseline visit: $25
- Final Study visit: $25

NEW INFORMATION
Sometimes during the course of a research study, new information becomes available about the treatment that is being studied. If new information comes out about uridine over the course of this study, your child's principal investigator will tell you about it and discuss with you whether or not you want your child to continue in the study.

NUMBER OF PARTICIPANTS
We expect to enroll 60 participants in this study, 40 participants with bipolar disorder and 20 participants without bipolar disorder, all at the University of Utah.

AUTHORIZATION FOR USE OF YOUR PROTECTED HEALTH INFORMATION
Signing this document means you allow us, the researchers in this study, and others working with us to use some information about your health for this research study.

This is the information we will use and include in our research records:

- Demographic and identifying information like name, date of birth, address, and telephone number.
- Related medical information about you like family psychiatric and medical history, current and past medications and therapies, and information from physical exams.
- All tests and procedures that will be done in the study.

How we will protect and share your information:

We will do everything we can to keep your information private but we cannot guarantee this. Study information will be kept in a secured manner and electronic records will be password protected. Study information may be stored with other information in your medical record. Other doctors, nurses, and third parties (like insurance companies) may be able to see this information as part of the regular treatment, payment, and health care operations of the hospital. We may also need to disclose information if required by law.

In order to conduct this study and make sure it is conducted as described in this form, the research records may be used and reviewed by others who are working with us on this research:

- Authorized members of the research team
- The University of Utah's Institutional Review Board (IRB), who reviews research involving people to make sure the study protects your rights.

If we share your information with groups outside of the University of Utah, we will not share your name or identifying information. We will label your information with a code number, so they will not know your identity.

If you do not want us to use information about your health, you should not be part of this research. If you choose not to participate, you can still receive health care services at University of Utah Sciences Center.

What if I decide to Not Participate after I sign the Consent and Authorization Form?

You can tell us anytime that you do not want to be in this study and do not want us to use your health information. You can also tell us in writing. . You must either give your revocation in person to the Principal Investigator or the Principal Investigator's staff, or mail it to Rebekah Huber at: The Brain Institute, 383 Colorow Dr., Salt Lake City, UT 84108. If you change your mind, we will not be able to collect new information about you, and you will be withdrawn from the research study. However, we can continue to use information we have already started to use in our research, as needed to maintain the integrity of the research.

This authorization does not have an expiration date.

You have a right to information used to make decisions about your child's health care. However, your child's information from this study will not be available during the study; it will be available after the study is finished.

CONSENT:

I confirm that I have read this parental permission document and have had the opportunity to ask questions. I will be given a signed copy of the parental permission form to keep.

I agree to allow my child to participate in this research study and authorize you to use and disclose health information about my child for this study, as you have explained in this document.

_____
Child's Name

_____
Parent/Guardian's Name

_____ _____
Parent/Guardian's Signature Date

_____
Relationship to Child for Parent/Guardian

_____
Name of Person Obtaining Authorization and Consent

_____ _____
Signature of Person Obtaining Authorization and Consent Date

Assent to Participate in a Research Study

Who are we and what are we doing?
We are from the Brain Institute of the University of Utah. We would like to ask if you would like to be in a research study. A research study is a way to find out new information about something.

Why are we asking you to be in this research study?
We are trying to find out if the investigational drug uridine can help depressed adolescents and young adults with bipolar disorder, when compared to taking a placebo. A placebo is a substance that contains no active ingredient, but looks exactly like the real drug. The reason for asking you to participate is because you do not have bipolar disorder.

This study will use questionnaires and tests of attention and memory to understand more about bipolar disorder. We will compare the results of youth with bipolar disorder to the results of youth without bipolar disorder.

What happens in the research study?
If you decide to be in this research study and your parent or guardian agrees, this is what will happen:

- We will ask you questions to make sure that you do not have any psychiatric or medical illnesses
- We will ask you to complete learning, attention, and memory tasks at the beginning and the end of the study. Some of these tasks will be done on a computer.
- We will give your teacher checklists to rate your current academic performance.

The research study may be stopped before you finish it. If this happens, you will be told why. You may also be asked to stop being in the study if you are not following the directions from the principal investigator.

Will any part of the research study hurt you?
The tests are considered painless.

Will the research study help you or anyone else?
The study may help doctors understand bipolar disorder, so that future patients will receive better treatment. This study may help doctors understand if uridine works for adolescents with bipolar disorder.

Who will see the information about you?
Only the researchers or others who are doing their jobs will be able to see the information about you from this research study. We will talk about this information with you, your doctors, and your parents. All of the information we collect about you will be kept in a locked cabinet or on computers that are protected by passwords. If you tell us that you want to hurt yourself, we will tell other adults about it so that we can help you feel better. We have to disclose information to those necessary if you tell us that you have been abused or intend to hurt others or yourself.

What if you have any questions about the research study?
You can ask any question you want about the study. If you have a question later that you didn't think of now, you can call me (Rebekah Huber) or ask me next time. You may call me to ask questions about your disease or treatment. My phone number is: (801)587-1439 or (385) 228-3560. You can also call Dr. Kondo at (801) 258-1659. He can be paged by contacting the hospital operator, at (801) 583-2500, and someone will answer 24 hours per day, including weekends and holidays.

Do you have to be in the research study?
You do not have to be in this study if you don't want to. Being in this study is up to you. No one will be upset if you don't want to do it. Even if you say yes now, you can change your mind later and tell us you want to stop. Please talk this over with your parents or guardians before you decide whether or not to participate. We will also ask your parents or guardians to give their permission for you to take part in this study. But even if your parents or guardians say "yes," you can still say "no" and decide not to do this.

There are alternatives to being in this study. You and your family can choose to not participate.

Agreeing to be in the study
I was able to ask questions about this study. Signing my name at the bottom means that I agree to be in this study. My parent or guardian and I will be given a copy of this form after I have signed it.

_____
Printed Name

_____ _____
Sign your name on this line Date

_____
Printed Name of Person Obtaining Assent

_____ _____
Signature of Person Obtaining Assent Date

The following should be completed by the study member conducting the assent process if the participant agrees to be in the study. Initial the appropriate selection:

_____ The participant is capable of reading the assent form and has signed above as documentation of assent to take part in this study.

_____ The participant is not capable of reading the assent form, but the information was verbally explained to him/her. The participant signed above as documentation of assent to take part in this study.

APPENDIX B

ACADEMIC EXPERIENCE AND EDUCATIONAL HISTORY

REPORT FORM

Academic and Education History Report Form

Baseline Visit

Participant ID: _____ Date: _____
Name: _____

Current Education Program: _____

Current Academic Status in Program: (check one)

- ☐ Currently enrolled in an education program
- ☐ On break from an education program
- ☐ Completed an education program
- ☐ Did not complete an education program
- ☐ Enrolled in alternative education program

Teacher to Rate Current Academic Performance: _____

Total Number of Years of Education: _____

Highest Education Program Completed: _____

Discontinued an Education Program? Yes No

Reason: _____

_____

Related to a mood episode? Yes No Extreme mood episode? Yes No

Experience(d) academic difficulties? Yes No When: _____

Explain (type, problem, frequency, and duration): _____

_____

_____

_____

Related to a mood episode? Yes No Extreme mood episode? Yes No

Receive Special Education Services at School? Yes No When: _____

Have an IEP? Yes No Have a 504 Plan? Yes No

Explain: (classification, services provided): _____

_____

_____

Related to a mood episode? Yes No Extreme mood episode? Yes No

Attend(ed) Alternative School/Programs? Yes No Type: _____

Reason: _____

_____

Related to a mood episode? Yes No Extreme mood episode? Yes No

Taken a Break from School? Yes No

Reason: _____

_____

Related to a mood episode? Yes No Extreme mood episode? Yes No

Transferred to a Different School/Program/University? Yes No

Reason: _____

_____

Related to a mood episode? Yes No Extreme mood episode? Yes No

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